

# NEUROPATHIC PAIN



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Welcome to the tenth issue of *Challenges in Neuropathic Pain*, a newsletter from the Multidisciplinary Panel on Neuropathic Pain. This newsletter comes at an exciting time for the panel, with the recent launch of their Web site at [www.neuropainhk.org](http://www.neuropainhk.org). Recommendations on various neuropathic pain syndromes, back issues of *Challenges in Neuropathic Pain* and patient education materials may be downloaded from the site. In this issue of the newsletter, there is a summary of the recommendations from the MPNP on the management of neuropathic cancer pain, as well as a number of articles to provide pertinent updates on neuropathic pain.

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## Recommendations on the Management of Neuropathic Cancer Pain

Pain can be a persistent and incapacitating symptom of cancer. Although reports indicate that only 15% of patients with nonmetastatic disease experience tumour-associated pain at the time of diagnosis, pain becomes more pervasive as disease progresses.<sup>1</sup> In patients with recurrent or metastatic cancer, 67% complain of pain and 41% experience pain directly attributable to the disease.<sup>2</sup>

Cancer-associated pain may be secondary to antineoplastic therapy or an unrelated comorbid condition, but is commonly due to direct tumour involvement (ie, infiltration or compression of adjacent local structures, such as bone, soft tissue, the gastrointestinal tract or nerves).<sup>1,3</sup> Hence, cancer pain syndromes can be somatic, visceral or neuropathic in origin.<sup>3,4</sup>

This set of recommendations aims to provide a logical approach to effectively manage cancer pain, with a particular focus on neuropathic pain. However, as patients may have several cancer pain syndromes that respond differently to pharmacological and nonpharmacological interventions, a pain management programme should be devised on an individual basis depending upon patient characteristics and responses.<sup>5,6</sup> Multiple medications may be required, with each agent adjusted according to the specific pain syndrome for which it is used.<sup>5</sup> Pain management should be guided by a detailed patient assessment.

### Assessment

- A detailed history and medical and physical examination should be performed to characterize and quantify pain, and to assess the primary cancer site and its relationship with the pain.<sup>4</sup>
- All components of pain (ie, intensity, character, location, radiation, timing, correlated factors and effects on daily living) should be assessed to assist in identifying specific pain syndromes and monitoring progression and response.<sup>1</sup>
- If neuropathic pain is present, nerve compression should be ruled out as this requires immediate action.<sup>5</sup> Imaging, such as magnetic resonance imaging (MRI), assesses the anatomical integrity of neural structures and may assist in localizing compression sites and planning treatment, especially when interventional therapies are being considered.<sup>7</sup> Analgesics should be instituted as early as possible even though full diagnosis may not yet be established.<sup>1,8</sup>
- Pain assessment should be repeated at regular intervals.<sup>1</sup> New reports of pain should be noted.

### Management

#### General principles of cancer pain treatment

- Cancer treatments, such as surgery, chemotherapy or radiotherapy, may relieve pain by reducing the size of the tumour and reducing compression or infiltration.<sup>1,3,9</sup>

- Nonsteroidal anti-inflammatory drugs may have a role in managing somatic cancer pain, particularly for patients with bone metastasis.<sup>5</sup>
- Pain caused by soft-tissue infiltration, visceral distention and increased intracranial pressure may initially be treated with corticosteroids (dexamethasone 4 to 8 mg, methylprednisolone 16 or 32 mg, or prednisone 20 to 40 mg) bid to tid.<sup>10</sup> Acute spinal cord compression should be treated with intravenous dexamethasone (10 to 20 mg) or methylprednisolone (40 to 80 mg) every 6 hours for several days, then gradually tapered to the minimum effective dose. Palliative surgical decompression of brain or spinal cord and fixation of painful spinal fractures are options in selected cases.
- Analgesics may be instituted in a stepwise fashion according to response (Figure). However, pain that is moderate to severe at the outset should be treated with potent opioids or a higher dose of non-opioid analgesic.<sup>9</sup>
- Adjunctive therapies may be used with or without conventional analgesics (Table).
- Patients who do not respond to adequate drug therapy may benefit from interventional therapy (Figure).<sup>4</sup> Candidates for interventional strategies should be carefully assessed.<sup>11</sup> The choice of therapy should be based on therapeutic goals and characteristics of the disease and the patient (eg, tumour characteristics, benefit-risk analysis, likely duration of survival and anticipated duration of hospitalization).<sup>1,8</sup>
- Physiotherapy techniques may decrease the need for analgesics<sup>1</sup>; however, they should not be a substitute for medication. They should be introduced early to treat generalized weakness, deconditioning and pain associated with inactivity and immobility. Psychological therapies such as cognitive-behavioural techniques should be instituted early in the course of the disease 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; other psychosocial and spiritual issues may 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.

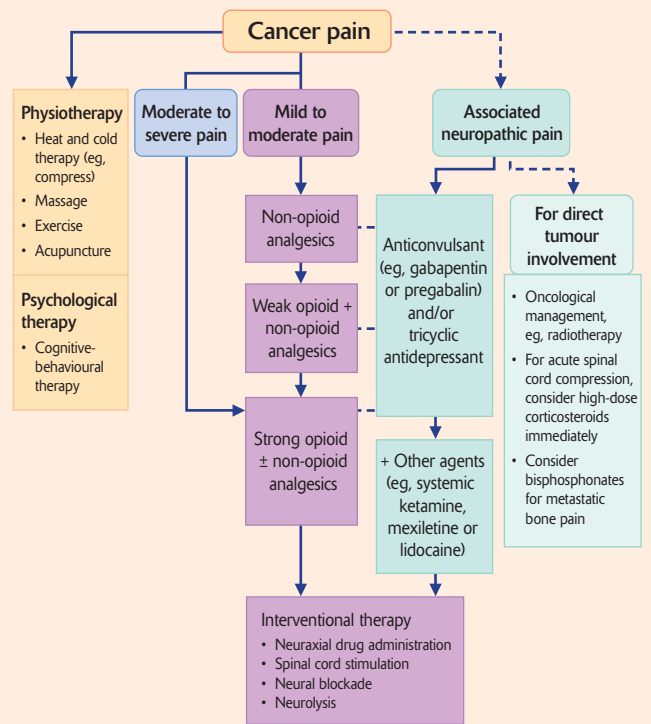
### For neuropathic cancer pain

- For neuropathic pain caused by direct tumour involvement, first-line management is oncological treatment and may include surgery, radiation therapy or chemotherapy.<sup>12</sup> For example, radiotherapy can relieve neuropathic pain due to tumour-induced neural compression or irritation.<sup>13</sup>
- Correctable causes of neuropathic pain (eg, spinal cord compression) should be managed appropriately.
- Anticonvulsants should be considered if neuropathic pain is unresponsive to conventional analgesics (Figure). Neuropathic pain specifically due to cancer treatment may be treated with gabapentin 300 mg tid after slow up-titration.<sup>14</sup> Dose may be adjusted according to response. Pregabalin, a novel anticonvulsant with analgesic and anxiolytic activity, is also effective for various neuropathic pain syndromes<sup>15</sup> and may be considered for neuropathic cancer pain. Anticonvulsants should be initiated at a low dose and slowly titrated until the patient achieves adequate pain relief or side effects develop.<sup>5</sup>
- Antidepressants such as tricyclic antidepressants or selective serotonin reuptake inhibitors are alternative options for management of neuropathic pain.<sup>16,17</sup> Antidepressants may be given together with anticonvulsants when there is unsatisfactory response to either medication.<sup>18</sup> Ketamine may be effective, but because of its adverse

effects should be limited to experienced teams.<sup>3,11</sup> Other adjunctive therapies include systemic lidocaine and mexiletine.<sup>5</sup>

- Interventional therapy may also be effective for neuropathic cancer pain.<sup>4</sup> However, certain interventional techniques for neuropathic pain should only be considered when pharmacological interventions have failed, are poorly tolerated or inappropriate.<sup>9</sup>
- Patients with postsurgical neuropathic pain may also benefit from topical capsaicin cream when appropriate.<sup>19</sup>

**Figure. Management of cancer pain**



Adapted from references 1,4,5,8-12,14,15.

**Table. Indications for adjunctive therapy<sup>1,3,4,8-10,15</sup>**

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

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## CASE PRESENTATION

*In each issue, a case study is presented on a relevant neuropathic pain syndrome. Reviewing case studies will help to improve your diagnostic approach to neuropathic pain and increase your understanding of how to select treatment strategies based on presenting symptoms. In this issue, a case of sciatica is discussed.*

# Sciatica

## Presenting symptoms

A 50-year-old male developed sudden-onset, sharp, low back pain during a game of tennis. The pain radiated down the back of his thigh and to the big toe, and was exacerbated by coughing and sneezing. There were no associated bowel or urinary symptoms.

## Objective findings

Clinical examination revealed lumbar paraspinal muscle spasm and tenderness. The patient had impaired straight leg raising, but power and sensation of lower limb muscles were intact.

## Management

The patient was treated with physiotherapy, transcutaneous electrical nerve stimulation and diclofenac SR 100 mg daily. Two weeks after the onset of his sciatic pain, he received epidural



Typical MRI of a patient with L4/L5 prolapsed intervertebral disc

steroid injections with methylprednisolone 80 mg on two occasions over a 3-week period. The injections reduced his pain after 2 days, improving his ability to perform physiotherapy exercises.

## Discussion

Sciatica results from irritation of the sciatic nerve when it is stretched or impinged, usually by a prolapsed intervertebral disc. However, it can also be caused by spondylolisthesis, spinal stenosis, malignant tumour, infection or piriformis syndrome. Serious aetiologies should be ruled out in patients who are young or elderly, have received recent steroid therapy, have a history of cancer, recent trauma to the back, fever, recent weight loss, acute worsening of chronic pain, bowel or urinary incontinence, increasing weakness of the lower limbs or ascending limb numbness. MRI is the most helpful investigative procedure.

Initial management includes reassuring patients and advising them to stay active and to avoid unnecessary back strain. If pain persists despite therapy with nonsteroidal anti-inflammatory drugs, referral to a physiotherapist should be considered, as well as treatment with tricyclic antidepressants or anticonvulsants. Epidural steroid or nerve root injection may provide short-term relief for severe and disabling pain. Orthopaedic referral is advisable for patients with severe symptoms, as surgery may be required to relieve neural compression or to treat the cause of the sciatica.

Source: MPNP members

## DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

*Various classes of drug may be used for the treatment of neuropathic pain. In the first in a series, we review the evidence for and role of anticonvulsants in treating neuropathic pain. In subsequent issues, we will review other drug classes including tricyclic antidepressants and opioids.*

## Part 1 – Anticonvulsants

Neuropathic pain responds poorly to conventional pain therapies and standard opioid doses. However, increased understanding of its pathogenesis has led to the development of a number of therapeutic options.

Whether peripheral or central in origin, neuropathic pain is characterized by neuronal hyperexcitability in damaged areas of the nervous system.<sup>1</sup> Neuronal hyperexcitability is caused by molecular changes at the peripheral nociceptor, the dorsal root ganglia, the spinal dorsal horn and the brain. As these changes also occur in patients with epilepsy, anticonvulsants may also be used for managing neuropathic pain.

Carbamazepine and phenytoin were the first anticonvulsants evaluated for neuropathic pain syndromes in controlled clinical trials. However, gabapentin has the most clearly documented analgesic effect.<sup>2</sup> It binds to the  $\alpha_2$ - $\delta$  subunit of voltage-dependent calcium channels at the postsynaptic dorsal horns,<sup>3</sup> interrupting a series of events that possibly lead to neuropathic pain sensation. Gabapentin is well tolerated, with dizziness and somnolence the most common adverse effects.<sup>2</sup> It is approved in several countries for the treatment of neuropathic pain syndromes.

Newer anticonvulsant drugs have also been evaluated. The evidence for lamotrigine is limited and conflicting,<sup>4</sup> while studies with topiramate in patients with diabetic neuropathy have shown mixed results.<sup>5</sup> Further randomized controlled trials are needed to confirm these observations.

Pregabalin, a novel drug, is another anticonvulsant with analgesic and anxiolytic activity. It is an analogue of the neurotransmitter  $\gamma$ -aminobutyric acid and, like gabapentin, binds to the  $\alpha_2$ - $\delta$  subunit of voltage-dependent calcium channels.<sup>3,6</sup> By binding to the  $\alpha_2$ - $\delta$  subunit, pregabalin reduces calcium influx at nerve terminals, hence reducing the release of several neurotransmitters, including glutamate, norepinephrine and substance P. Pregabalin has a predictable pharmacokinetic profile, few drug interactions and a rapid onset of action. It is effective in animal models of neuropathic pain<sup>7,8</sup> and in patients with painful diabetic neuropathy<sup>6</sup> and postherpetic neuralgia.<sup>9</sup>

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## LITERATURE REVIEW

Freyenhagen R, Strojek K, Griesing T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomized, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 2005;115:254-263.

Previous clinical trials have demonstrated the efficacy of pregabalin for the treatment of painful diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). Pregabalin, a selective ligand with high-affinity for the  $\alpha_2\text{-}\delta$  subunit of voltage-gated calcium channels, modulates neuropathic pain by reducing calcium-mediated neurotransmitter release.

This 12-week, randomized, multicentre, parallel-group, placebo-controlled study compared the efficacy and safety of two dosing regimens of pregabalin in 338 patients with chronic neuropathic pain due to DPN and PHN. Patients were randomized to placebo (n=65), flexible-dose pregabalin (150-600 mg/day, titrated at weekly intervals according to response and tolerability; n=141) or fixed-dose pregabalin (300 mg/day during week 1 and 600 mg/day thereafter; n=132) in a double-blind design. Patients used a diary to record pain and pain-related sleep interference on 11-point numerical rating scales (NRS). The primary efficacy parameter was endpoint mean pain score based on NRS. Secondary endpoints included sleep interference and the Patient Global Impression of Change (PGIC).

Compared with placebo, flexible- and fixed-dose pregabalin regimens significantly reduced endpoint mean pain score (p=0.002 and p<0.001, respectively) and improved pain-related sleep interference (p<0.001). A significantly greater proportion of patients in the flexible- and fixed-dose pregabalin groups achieved a  $\geq 50\%$  reduction in mean pain score from baseline compared with placebo (48.2%, 52.3% and 24.2%, respectively; p<0.001 vs placebo). Furthermore, a statistically significantly greater proportion of patients in the pregabalin groups reported improvements in PGIC at endpoint than in the placebo group. The most common pregabalin-associated adverse events were dizziness (23.8%), weight gain (12.8%), peripheral oedema (11.7%) and somnolence (11.7%).

This study shows that flexible- and fixed-dose pregabalin regimens are effective and well tolerated in the treatment of chronic neuropathic pain associated with DPN or PHN. Flexible dosing of pregabalin is recommended as it permits dosage adjustment for optimal efficacy and tolerability, and reflects the situation in routine clinical practice.

## Contact us

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## Q & A

E-mail your questions on neuropathic pain to the Multidisciplinary Panel on Neuropathic Pain at [mpnp@asia.cmpmedica.com](mailto:mpnp@asia.cmpmedica.com).

## What is phantom limb pain?

The amputation of an extremity or the transection of a peripheral nerve is almost invariably followed by the sensation of a phantom limb – the persistent sensation of the missing or denervated limb.<sup>1</sup>

Phantom limb sensations may or may not be painful.<sup>1</sup> Painful phantom limb sensations can be: 1) burning or throbbing; or 2) abnormal ischaemic discomfort.<sup>1</sup> Painful sensations are often intense, disrupting daily activities and causing depression and social isolation.<sup>1</sup> Phantom limb pain can also be a major obstacle to successful rehabilitation. Phantom pain is different from stump pain,<sup>2,3</sup> and causes of stump pain should be excluded during clinical assessment and before appropriate treatment is offered to the patient.

Several central and peripheral mechanisms have been postulated to explain phantom limb pain.<sup>1,3</sup> For example, postamputation peripheral damage to nociceptive fibres and dorsal root ganglion cells may cause abnormal sensitivity to mechanical, thermal and chemical stimuli. Alternatively, the degeneration of nociceptive neurons may trigger anatomical sprouting of low threshold mechanosensitive terminals to form connections with central nociceptive neurons and, subsequently, induce functional synaptic reorganization in the dorsal horn. Furthermore, prolonged sensitization of central nociceptive 'second order' neurons in the dorsal horn of the spinal cord may result in hyperexcitable nerves responsive to non-noxious stimuli.

Preventive measures for phantom limb pain include good preamputation pain control, precise surgical technique and subsequent surgical revision of stump aberrations, such as scar tissue, keloids, inadequate closure and poor wound healing.<sup>1</sup> Treatment options for phantom limb pain include pharmacotherapy, such as anticonvulsant drugs, antidepressants, baclofen, calcitonin, capsaicin, anaesthetics or opioids.<sup>1,2</sup> Transcutaneous electrical nerve stimulation is effective in some patients.<sup>1,2</sup> Neurosurgical techniques are considered a last resort.<sup>1</sup> Psychological therapy may be useful in alleviating the psychological factors (eg, stress and depression) that can influence the severity of phantom limb pain.<sup>1</sup> However, complete pain relief is unlikely in some patients with chronic phantom limb pain.<sup>1</sup> In such patients, a cognitive-behavioural-based pain management programme may be helpful to teach patients how to reduce the impact of the pain on their life, and to improve function, mood, sleep and overall quality of life.

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