PAIN MANAGEMENT

Recommendations on the Management of Neuropathic Cancer Pain

The Multidisciplinary Panel on Neuropathic Pain
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This is an update of the recommendations on neuropathic cancer pain management written by members of the Hong Kong–based Multidisciplinary Panel on Neuropathic Pain.

Panel on Neuropathic Pain in 2006,1 aim to provide a logical approach to effectively manage cancer pain, with a particular focus on neuropathic pain.

Prevalence, Pathophysiology and Symptoms

Pain is prevalent in cancer patients and is often difficult to treat, especially neuropathic cancer pain. Neuropathic cancer pain often responds poorly to opioids; hence, the use of adjuvant medications is necessary. Patients who do not experience sufficient pain relief with pharmacological therapy may benefit from interventional therapies. These recommendations, which are an update of those first published by the Multidisciplinary Panel on Neuropathic Pain in 2006, aim to provide a logical approach to effectively manage cancer pain, with a particular focus on neuropathic pain.

Prevalence, Pathophysiology and Symptoms

Pain can be a persistent and incapacitating symptom of cancer. An international survey on cancer pain by the International Association for the Study of Pain revealed that in this sample, around 90% of patients experienced pain, of which 40% was caused by neuropathic mechanisms.2 Cancer pain may be chronic or acute, and patients with chronic pain commonly experience acute flares of pain. One-half to two-thirds of patients with well-controlled chronic pain experience transitory ‘breakthrough’ pain.3

Cancer-associated pain may be secondary to anti-neoplastic therapy or an unrelated co-morbid condition but is commonly due to direct tumour involvement (ie, infiltration
or compression of adjacent local structures, such as bone, soft tissue, nerves or the gastrointestinal tract.\(^3\)\(^,\)\(^5\)

Hence, cancer pain syndromes can be somatic, visceral or neuropathic in origin.\(^3\) Understanding and recognizing these syndromes can help identify pain aetiology and the need for additional evaluation, and target therapy more appropriately.

**Types of Pain**

Somatic pain originates from disorders of bone, joints, muscles or connective tissue.\(^3\) Bone pain syndromes are the most prevalent,\(^3\)\(^,\)\(^5\) while somatic pain from other sites is due to continuous peripheral nociceptor stimulation such as by inflammatory mediators, muscle spasms, postsurgical incisions, and radiotherapy or chemotherapy.

Visceral pain is caused by obstruction, infiltration or compression of visceral structures and supporting connective tissues.\(^3\) 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,\(^3\) characterized by aching, burning, stabbing or lancinating pain,\(^3\)\(^,\)\(^6\)\(^,\)\(^9\) and may also present as paraesthesia, dysesthesia, hyperalgesia or allodynia. It occurs in approximately 30–55% of cancer patients, although recent estimates in patients with head and neck cancer varied from 34% to 73%.\(^7\)\(^,\)\(^8\)

Neuropathic pain is often due to tumour infiltration or compression of neural structures,\(^3\)\(^,\)\(^6\)\(^,\)\(^9\) while sympathetic activity also plays a role in spontaneous neuropathic pain.\(^3\) In addition, most post-treatment pain syndromes (eg, post-surgical, post-radiotherapy or post-chemotherapy pain) are neuropathic.\(^3\) Relative to somatic and visceral pain, neuropathic pain responds poorly to systemic opioids; hence, other treatments are often utilized.\(^3\)\(^,\)\(^10\)\(^,\)\(^11\)

**Assessment**

- 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.\(^3\)
- All components of pain (eg, intensity, characteristics, location, radiation, timing and effect on daily living) should be assessed to identify specific pain syndromes and monitoring progression and response.\(^4\)
- Clinical assessment of neuropathic cancer pain may be challenging; currently no single method is available to reliably diagnose cancer-related neuropathic pain.\(^12\) However, a number of screening tools are available to help identify neuropathic pain. The ID 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.\(^14\)

**Management**

**General Principles of Cancer Pain Treatment**

- Cancer treatments, such as surgery, chemotherapy or radiotherapy, may relieve pain by removing or reducing the size of the tumour and reducing compression or infiltration.\(^17\)
- Non-steroidal anti-inflammatory drugs (NSAIDs) may have a role in managing somatic cancer pain, particularly for patients with bone metastasis.\(^10\)\(^,\)\(^16\)
- Pain caused by soft-tissue infiltration, visceral distention and increased intracranial pressure may be treated initially with corticosteroids.\(^18\)
- 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).\(^11\)\(^,\)\(^16\)

"Currently no single method is available to reliably diagnose cancer-related neuropathic pain"
that is moderate to severe at the outset should be treated with higher-potency opioids or with higher doses.\(^\text{17}\)

- Adjunctive therapies may be used with or without conventional analgesics at any stage (Table).\(^\text{19}\)
- Patients who do not respond to adequate drug therapy may benefit from interventional techniques (Figure).\(^\text{3}\) The choice of therapy should be based on therapeutic goals and characteristics of the disease and the patient (eg, type of tumour, benefit-risk analysis, anticipated duration of hospitalization and likely duration of survival).\(^\text{4,16}\)
- Physiotherapy may reduce the need for analgesics.\(^\text{4}\) However, 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 techniques, should 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.

### For Neuropathic Cancer Pain
- About 50% of all difficult to control cancer pain is neuropathic.\(^\text{11}\) For neuropathic pain caused by direct tumour involvement, first-line management may include surgery, radiation therapy or chemotherapy.\(^\text{20}\)
- Correctable causes of neuropathic pain (eg, spinal cord compression) should be managed appropriately.

| Table. Indications for adjunctive therapy\(^\text{6,11,16–19}\) |
|---------------------------------|---------------------------------|
| **Indication** | **Adjunctive therapy** |
| Neuropathic pain | Anticonvulsants (eg, gabapentin, pregabalin) |
| | Antidepressants (eg, amitriptyline, venlafaxine) |
| | Other agents (eg, ketamine, mexiletine, lidocaine) |
| Metastatic bone pain | Bisphosphonates (eg, pamidronate) |
| Anxiety symptoms | Hydroxyzine |
| Emesis | Hydroxyzine |
| Poor analgesic response | Corticosteroids |
| Increased intracranial pressure | Corticosteroids |
| Spinal cord compression | Corticosteroids |
| Perineural oedema and nerve compression | Corticosteroids |
| Nausea | Corticosteroids |
| Anorexia and poor appetite | Corticosteroids |
| Cachexia | Corticosteroids |
• Anticonvulsants (eg, gabapentin, pregabalin) and antidepressants (eg, amitriptyline, venlafaxine) are recommended adjuvant analgesics for cancer-related neuropathic pain (Figure).9,21,22 A recent systematic review revealed that the use of antiepileptic and antidepressant agents as adjuvants to opioids improved pain control, although there is potential for an increase in side effects.23 The strongest evidence is for gabapentin.23,24 However, data from the United States revealed that the use of these types of drugs is relatively low in neuropathic cancer pain.25

• Ketamine may be effective but, because of its adverse effects, should be limited to experienced teams.5,20 Other adjunctive therapies include systemic or topical lidocaine and topical capsaicin.8,27,28

• A recent prospective study in 818 patients with neuropathic cancer pain revealed that pain could be relieved by multimodal treatment following the WHO analgesic ladder in the majority of patients; the main adjuvant drugs were amitriptyline, gabapentin, dexamethasone.29

• Interventional therapy may also be effective for neuropathic cancer pain.30–36 However, certain interventional techniques for neuropathic pain should only be considered when pharmacological interventions have failed, are poorly tolerated, or are inappropriate.17

Ongoing assessment and communication with patients are 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.37

Undermanagement
Despite the presence of cancer pain guidelines, such as those from the WHO, cancer pain is often undertreated. A large-scale study on patients with recurrent or metastatic cancer revealed that 42% of patients suffering from pain received inadequate analgesia.38 This may be because of inadequate knowledge of pain management, poor pain assessment, reluctance to use analgesics, and restrictive analgesic regulations.4,38

Adherence to the WHO analgesic ladder is associated with some shortcomings in clinical practice. Twenty-five percent of patients treated with basic analgesics actually had moderate to severe pain that should have been treated with more potent analgesics.4 Other authors suggested that since certain analgesics may be more useful for particular pain conditions, a more mechanistic approach may have a role in drug selection, especially in pain that involves multiple mechanisms or is poorly responsive to conventional therapies, such as neuropathic pain.5,20 However, as described above, neuropathic cancer pain can be relieved by multimodal treatment following the WHO analgesic ladder in the majority of patients.29

Declaration of Interests
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Appendix. Evidence-based management of neuropathic cancer pain

Pharmacotherapy

I. Opioids
Evidence supports the role of opioids for other neuropathies such as postherpetic neuralgia and central or peripheral neuropathic pain. However, the effectiveness of opioids for neuropathic pain is controversial. While some literature suggests that the response of neuropathic pain to opioids is suboptimal, this may be relative and not due to reduced opioid sensitivity. Instead, there may be failure to deliver a sufficiently high concentration of systemic opioid to the spinal cord without causing adverse effects.

Despite the reliance on opioids, adherence to the WHO guidelines provides equally effective analgesia regardless of the pain mechanism. Owing to mixed pain mechanisms in many cancer patients, one review suggested that patients may require both opioids and NSAIDs, in addition to specific neuropathic pain agents, to achieve acceptable pain relief.

Transdermal buprenorphine is a further option for neuropathic cancer pain. A recent expert panel consensus statement indicated that transdermal buprenorphine was a valuable treatment for chronic cancer pain, including neuropathic cancer pain. It has good efficacy and an acceptable safety and tolerability profile, including a low risk of respiratory depression, a lack of immunosuppression and a lack of accumulation in patients with impaired renal function.

Tramadol may also be an effective therapeutic option for neuropathic cancer pain. In a double-blind, placebo-controlled study (n = 36), patients receiving tramadol had major improvements in pain intensity (P < 0.001), improved sleep quality by day 45 (P < 0.05), improved activities of daily living (P < 0.05) and reduced use of analgesics (P < 0.05) compared with placebo. However, the tramadol group was associated with more adverse events (P < 0.05), most commonly nausea, vomiting and constipation. In addition, care must be taken when using tramadol in combination with selective serotonin reuptake inhibitors, such as venlafaxine and duloxetine, and selective serotonin and norepinephrine reuptake inhibitors, as this may increase the risk of serotonin syndrome; tramadol may also increase the risk of seizure. There is some evidence that methadone may be effective for neuropathic cancer pain.

II. Anticonvulsants
While opioids are the usual first-line treatments for moderate to severe cancer pain in general, neuropathic cancer pain responds less reliably than other pain types. Anticonvulsants may be used as adjunctive therapy for neuropathic cancer pain, especially for patients with lancinating pain or those poorly responsive to opioid therapy. Anticonvulsant use may decrease opioid dose and, hence, associated side effects.

Gabapentin has established efficacy in a variety of neuropathic pain syndromes, including neuropathic cancer pain. A multicentre, randomized, double-blind, placebo-controlled trial demonstrated that gabapentin was effective in treating neuropathic cancer pain. Compared with placebo, gabapentin-treated patients had significantly lower global pain scores (4.6 vs 5.4; P = 0.025), and less dysesthesia (4.3 vs 5.2; P = 0.0077) when measured on a 0–10 numerical scale.

More recently, studies have demonstrated that gabapentin provides additional pain relief as an adjuvant analgesic in neuropathic cancer pain when combined with opioids. In another study, low-dose gabapentin (200 to 400 mg/day) combined with the antidepressant imipramine (20 mg/day) in patients with neuropathic cancer pain significantly decreased total pain score and daily paroxysmal episodes compared with either drug alone.

While effective in a number of neuropathic pain conditions, there are few studies yet on pregabalin in neuropathic cancer pain. A case report in a patient with pancreatic cancer and oxaliplatin-induced hyperexcitability syndrome revealed that pregabalin reduced the symptoms of this syndrome. A study in 39 patients with continuous epidural analgesia for chronic cancer pain demonstrated that pregabalin lowered the visual analog scale (VAS) score from 5.3 ± 0.4 to 2.9 ± 0.2 (P < 0.01) and improved quality of life significantly (P < 0.05) after just 2 days of treatment.

Older anticonvulsants, such as phenytoin and carbamazepine, have also been used traditionally for analgesia. However, their adverse effect profiles are less favourable than gabapentin, and evidence supporting their efficacy in neuropathic cancer pain is lacking. Topiramate may provide benefit as a second- or third-line treatment.

Anticonvulsants for Post-treatment Neuropathic Pain
Gabapentin may also relieve neuropathic pain due to anticancer therapy. An open-label exploratory non-controlled study involving cancer outpatients without active disease and with chronic, treatment-related pain (n = 23) demonstrated that gabapentin reduced pain intensity (P < 0.01) and increased pain relief from 8.3% to 66.6% (P < 0.01).

III. Antidepressants
Antidepressants are recommended for the management of many types of neuropathic pain. Antidepressants are also commonly recommended as adjunctive therapy for neuropathic cancer pain, especially for patients with continuous dysesthesia. These agents provide analgesia, potentiate the effect of opioids, and reduce depression and insomnia.

Although commonly used in practice, there is limited evidence from controlled trials evaluating the analgesic efficacy of tricyclic antidepressants in cancer patients. One randomized, double-blind, placebo-controlled, crossover trial (n = 16) showed that short-term amitriptyline as add-on therapy to morphine therapy for cancer patients with moderate neuropathic pain did not significantly improve global pain intensity and quality-of-life scores, and failed to reduce opioid requirements; there was a significant difference in worst pain (P < 0.035). However, this study was limited by low patient numbers and a relatively short washout period (2 weeks).

Antidepressants for Post-treatment Neuropathic Pain
Antidepressants may be effective for neuropathic pain due to anticancer treatment. One randomized, controlled trial (n = 15) demonstrated that amitriptyline effectively reduced neuropathic pain following treatment of breast cancer, but adverse effects hindered its regular use. In contrast,
another randomized controlled trial in patients with chemotherapy-induced neuropathic pain (n = 44) reported that low-dose amitriptyline (10–50 mg/day) showed a trend for an improvement in neuropathic pain symptoms, but the authors felt that statistical significance was likely not reached owing to small patient numbers.67

Another study (n = 13) showed that maximum pain intensity was lower in patients treated with venlafaxine compared with placebo, and adverse effects from venlafaxine were similar to placebo.68

Pre-emptive Analgesia
A randomized, double-blind, trial (n = 114) on the efficacy of amitriptyline versus placebo in preventing chemotherapy-induced neuropathic symptoms found no difference between the groups.69

Following surgery for breast cancer, some patients develop post-mastectomy pain syndrome, a neuropathic pain syndrome. A double-blind, randomized study compared the efficacy of perioperative administration of venlafaxine (37.5 mg/day), gabapentin (300 mg/day) or placebo given for 10 days starting the night before surgery on the development of pain during the 6 months postoperatively.70 Both drugs reduced analgesic requirements following surgery, and at 6 months venlafaxine significantly reduced the incidence of post-mastectomy pain syndrome; gabapentin had no effect on chronic pain except for decreasing the incidence of burning pain.

IV. Anaesthetics, Anti-arrhythmic Agents and N-methyl-D-aspartate Receptor Antagonists
Anaesthetics may be used as primary therapy for treatment of cancer-associated neuropathic pain in some centres, whereas others use them as second-line agents.39 However, there is limited evidence supporting their use for cancer pain. There are a few reports that subcutaneous infusion of lidocaine 10% improved pain refractory to systemic and spinal opiates in patients with terminal malignancy.71 While a systematic review reported that although intravenous lidocaine was effective for non-cancer-related neuropathic pain, it had no effect on cancer-related pain.72 In contrast, a recently published case report concluded that intravenous lidocaine may have a role for severe cancer-related neuropathic pain at the end-of-life.73 Oral mexiletine showed some efficacy in pain due to peripheral nerve damage, but not for central pain.72 In a systematic review, lidocaine and oral analogues were better than placebo and were as effective as other analgesics in the treatment of neuropathic pain.74

Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, may reduce hypersensitivity in the dorsal horn, alleviate NMDA-related neuropathic pain, and has a synergistic effect with opioids in cancer pain patients that are unresponsive to high-dose morphine.5,75 However, because of its adverse effects, ketamine therapy should be instituted by experienced teams.76 A recent case report described the use of low-dose intravenous ketamine in an inpatient setting followed by the use of oral memantine for long-term outpatient management in an opioid-refractory oncology patient.76

Flupirtine, a non-opioid analgesic that acts as a functional NMDA receptor antagonist, showed some benefit in palliative care patients with neuropathic pain due to cancer.77 It may be useful in the treatment of neuropathic pain as an adjuvant to opioids.

V. NSAIDs and Corticosteroids
Although current cancer pain guidelines recommend the use of NSAIDs, there is little evidence supporting their role in treating the neuropathic component of cancer pain. Similarly, evidence supporting the use of corticosteroids for neuropathic cancer pain is lacking. However, corticosteroids are recommended for patients with acute nerve or spinal cord compression.10,18

VI. Topical Agents
The primary role of capsaicin in neuropathic cancer pain is in post-surgical neuropathic pain. A study involving cancer patients with post-surgical neuropathic pain (n = 99) showed that capsaicin 0.075% cream given for 8 weeks, four times daily, reduced pain by 53%, compared with a 17% reduction with placebo (P = 0.01).27 After the study period, significantly more patients indicated that capsaicin was the more beneficial treatment (60% vs 18% for placebo; P = 0.001).

Lidocaine patches are recommended for the treatment of some types of neuropathic pain, most notably postherpetic neuralgia.24,47 A retrospective audit of lidocaine 5% patch within a comprehensive cancer centre found that the data supported the trials of lidocaine 5% patch for cancer patients with neuropathic pain syndromes associated with allodynia.28 However, in cancer patients with post-surgical incisional neuropathic pain, a double-blind, randomized, cross-over study found that lidocaine 5% patches did not significantly reduce pain intensity ratings compared with placebo, but did improve some secondary outcomes including general activity (P = 0.02).78

Non-pharmacological Treatments
Most non-drug treatments for neuropathic cancer pain involve interventional therapy, as described below. While there is little data on the role of complementary therapy in the management of neuropathic cancer pain, a recent review article described that such treatments as massage, acupuncture, and psychological and behavioural approaches may be of use in the management of neuropathic cancer pain.79

Interventional Therapy
I. Neuaxial Drug Administration
Spinal analogesia effectively relieves refractory cancer pain and should be considered for patients with pain that is poorly responsive to administration of drugs via conventional routes, and those with poor tolerance to systemic medications.30,80,81 Intrathecal administration may minimize systemic absorption and related side effects after administration of higher doses, which may be required for opioid-resistant pain such as neuropathic cancer pain.91 Studies have shown that intrathecal opioids and intraspinal clonidine may be effective in neuropathic cancer pain.31,32 Spinal administration of other anaesthetics may be effective as an adjunct to intrathecal opioids, but efficacy in neuropathic cancer pain is anecdotal.82,83

II. Radiofrequency Treatment and Neurostimulation
Percutaneous electrical nerve stimulation has been useful for a small subset of cancer patients, such as those with opioid-resistant pain due to bony metastasis.84 However, evidence to support its use in neuropathic cancer pain is lacking.
Spinal cord stimulation (SCS) may be effective in a variety of neuropathic pain syndromes.\textsuperscript{85,86} A systematic literature review showed that although SCS is beneficial in vasculopathic and postherpetic neuralgia, it has no clinical usefulness in cancer pain.\textsuperscript{87} However, a recent publication has demonstrated that SCS provided pain relief in patients with cancer-related chest wall pain (n = 14).\textsuperscript{33}

Radiofrequency treatment combined with glucocorticoid in patients with refractory neuropathic pain following breast cancer surgery relieved pain and improved quality of life\textsuperscript{88}; however, further studies are necessary to evaluate the effectiveness of radiofrequency treatment in neuropathic cancer pain.

III. Neural Blockade
The literature on neural blockade via anaesthetic infusion to control neuropathic cancer pain shows favourable effects but is limited to case reports or by small sample sizes, probably because of the specificity of indications for these procedures.\textsuperscript{89,90} This may indicate a role in neuropathic pain control but highlights the need for careful patient assessment and selection to optimize outcomes.

IV. Neurolysis
Some cancer patients may benefit from neurolytic procedures, such as patients with severe, intractable pain that is responsive to diagnostic neural blockade but uncontrolled by less aggressive procedures owing to poor response or tolerance.\textsuperscript{91} A clinical review concluded that neurolytic sympathetic procedures for pancreatic and pelvic cancer may be useful for reducing pain when multiple pain mechanisms are involved.\textsuperscript{92} However, the literature on the use of neurolysis specifically for neuropathic cancer pain is scarce and suggests a limited role, with one review stating that peripheral neurolytic blocks may be helpful in some cancer patients with peripheral neuropathies.\textsuperscript{93}

References