



Recommendations on the Management of Neuropathic Cancer Pain

Multidisciplinary Panel on Neuropathic Pain*

I. Prevalence, Pathophysiology and Symptoms

Pain can be a persistent and incapacitating symptom of cancer. Although reports indicate only 15% of patients with nonmetastatic disease experience tumour-associated pain at the time of diagnosis, pain becomes more pervasive as disease progresses.¹ In patients with recurrent or metastatic cancer, 67% complain of pain and 41% experience pain directly attributable to the disease.² 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 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, nerves or the gastrointestinal tract).^{1,4} Hence, cancer pain syndromes can be somatic, visceral or

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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.

Somatic Pain

Somatic pain originates from disorders of bone, joints, muscles or connective tissue.³ Bone pain syndromes are the most prevalent and arise from stretching of the periosteum by an expanding tumour, local microfractures that cause bone distortion, direct tumour encroachment and local release of algescic substances from bone marrow.^{3,4} Somatic pain from other sites is due to continuous peripheral nociceptor stimulation by inflammatory mediators, reactive spasms of muscles overlying an area of tissue damage, postsurgical incisions and radiotherapy or chemotherapy.

Visceral Pain

Visceral pain is caused by obstruction, infiltration or compression of visceral structures and supporting connective tissues.³ Lung, liver and kidney parenchyma are insensitive to pain, but tumours associated with these organs may cause pain when the capsule or adjacent structures are affected.⁴ Visceral pain is often diffuse and sometimes referred to other nonvisceral structures, making the source of pain difficult to localize.

Neuropathic Pain

Studies indicate approximately 30% to 55% of cancer patients have neuropathic pain, which is due to involvement of neural structures (eg, nerves, plexi or roots), usually by tumour infiltration or compression.^{3,5,6} Sympathetic activity also plays a role in spontaneous neuro-

pathic pain.³ This type of pain is characterized as aching, burning, stabbing or lancinating.^{3,4} It may also present as paraesthesia, dysaesthesia, hyperalgesia or allodynia. Relative to somatic and visceral pain, neuropathic pain responds poorly to systemic opioids, hence other treatments are often utilized.^{4,7}

Most post-treatment pain syndromes (eg, postsurgical, post-radiotherapy or postchemotherapy pain) are neuropathic.³ Injury to the intercostobrachial nerve during mastectomy causes a tight, burning sensation in the axilla, the medial aspect of the upper arm and the upper aspect of the anterior chest wall. Radiation-induced fibrosis can cause peripheral nerve injury. Vincristine, cisplatin and paclitaxel are neurotoxic and can cause dysaesthesia, paraesthesia, cramps and restless legs associated with weakness, sensory loss or autonomic dysfunction.

This set of recommendations aims to provide a logical approach to effectively manage cancer pain, with a particular focus on neuropathic pain. Patients may have several cancer pain syndromes that respond differently to pharmacological and nonpharmacological interventions.^{7,8} Therefore, a pain management programme should be devised on an individual basis depending upon patient characteristics and responses. Multiple medications may be used, with each agent adjusted according to the specific pain syndrome for which it is used.⁷ Pain management should be guided by a detailed patient assessment.

II. Assessment

- A detailed history and medical, physical and neurological exami-

nation 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 assist in identifying specific pain syndromes and monitoring progression and response.¹
- If neuropathic pain is present, nerve compression should be ruled out, as this requires immediate action.⁷ Use of imaging, such as magnetic resonance imaging, assesses the anatomical integrity of neural structures and may assist in localizing compression sites and in treatment planning, especially when interventional therapies are contemplated.⁹ Analgesics should be instituted as early as possible even though full diagnosis is not yet established.^{1,10}
- Because of the progressive nature of most cancers and the alterations in cancer pain characteristics, assessment should be repeated at regular intervals.¹ New reports of pain should be noted.

III. Management

General Principles of Cancer Pain Treatment

- Cancer treatments, such as surgery, chemotherapy or radiotherapy, may relieve pain by inducing significant tumour shrinkage and reducing compression or infiltration.¹¹
- Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a role in managing somatic cancer pain,

- particularly for patients with bone metastasis.^{7,10}
- Pain caused by soft-tissue infiltration, visceral distention and increased intracranial pressure may be treated initially with corticosteroids (dexamethasone 4-8 mg, methylprednisolone 16 or 32 mg, or prednisone 20-40 mg) bid to tid.¹² Acute spinal cord compression should be treated with intravenous dexamethasone (10-20 mg) or methylprednisolone (40-80 mg) every 6 hours for several days, then gradually tapered to the minimum effective dose. Surgical decompression of the brain or spinal cord and fixation of painful spinal fractures should be considered where appropriate.
- 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 by higher potency opioids or with higher doses.¹¹
- Adjunctive therapies may be used with or without conventional analgesics. (Table)

- Patients who do not respond to adequate drug therapy may benefit from interventional techniques.³ (Figure) Candidates for interventional strategies should be carefully assessed.¹³ 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).^{1,10}
- Physiotherapy may decrease the need for analgesics.¹ However, physiotherapy should not be used as a substitute for medication, and 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 termi-

nal 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 this group of patients.

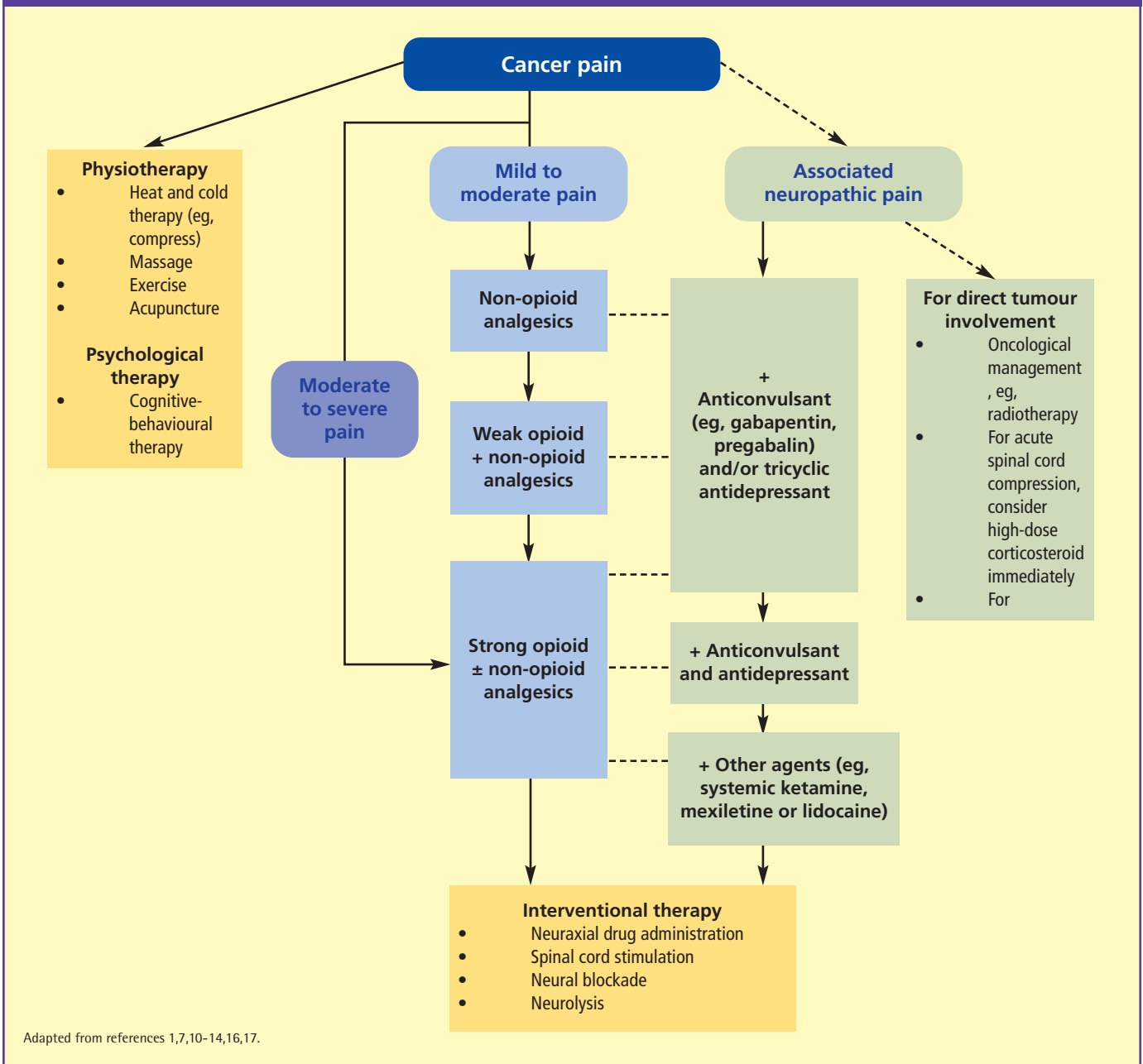
For Neuropathic Cancer Pain

- For neuropathic pain caused by direct tumour involvement, first-line management is oncological treatment and may include surgery, radiation therapy or chemotherapy.¹⁴ For example, radiotherapy can relieve neuropathic pain due to tumour-induced neural compression or irritation.¹⁵
- Correctable causes of neuropathic pain (eg, spinal cord compression) should be managed appropriately.
- Anticonvulsants (eg, gabapentin, pregabalin) should be considered if neuropathic pain is unresponsive to conventional analgesics. (Figure) They should be started at a low dose and slowly up-titrated until the patient achieves adequate relief or side effects develop.⁷ Antidepressants (eg, tricyclic antidepressants or selective serotonin reuptake inhibitors) may be given together with anticonvulsant therapy when there is a satisfactory response with either medication.¹⁶ Ketamine may be effective but, because of its adverse effects, should be limited to experienced teams.^{4,13} Other adjunctive therapies include systemic lidocaine and mexiletine.⁷
- Interventional therapy may also be effective for neuropathic cancer pain.¹⁷⁻²³ However, certain

Table. Indications for adjunctive therapy^{4,10,11,12,16}

Indication	Adjunctive therapy
Neuropathic pain	Anticonvulsants (eg, gabapentin) 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

Figure. Management of cancer pain.



interventional techniques for neuropathic pain should only be considered when pharmacological interventions have failed, or are poorly tolerated or inappropriate.¹¹

- Neuropathic pain specifically due to cancer treatment may be treated with gabapentin 300 mg tid after slow up-titration.²⁴ Dose may be adjusted according to response. Other therapeutic

options include antidepressants such as amitriptyline and venlafaxine.^{25,26} Patients with post-surgical neuropathic pain may also benefit from capsaicin cream, when appropriate.²⁷

Appendix 1: Evidence-based Management of Neuropathic Cancer Pain

Pharmacotherapy

I. Opioids

There is evidence to support the role of opioid analgesics for other neuropathies such as postherpetic neuralgia.^{28,29} Likewise, another randomized, controlled trial showed low-dose levorphanol (maximum daily dose=3.15 mg) reduced pain intensity scores by 21% in patients with central or peripheral neuropathic pain, while high-dose therapy (maximum daily dose=15.75 mg) reduced pain scores by 36%.³⁰

The efficacy of opioids for neuropathic pain is controversial. While some literature suggests the response of neuropathic pain to opioids is suboptimal, this may be relative and not due to reduced opioid sensitivity.^{1,4,7,31-33} Instead, there may be failure to deliver a sufficiently high concentration of systemic opioid to the spinal cord without causing adverse effects.⁴

Despite the reliance on opioids, adherence to the WHO guidelines provides equally effective analgesia, whether the pain is neuropathic, nociceptive or mixed, in most patients (with over 80% of patients rating their pain as less than moderate), regardless of the pain mechanism.^{8,13} Due 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.⁷

Furthermore, a small study suggested methadone may be effective for neuropathic cancer pain.³⁴ When cancer and noncancer patients with neuropathic pain (n=18) were treated with a median stable dose of methadone 15 mg/day, the mean pain intensity score (measured by the visual analogue scale) was reduced from 7.7 to 1.4 ($p<0.0001$). Seventy percent of patients with mechanical allodynia and all patients with shooting pain experienced complete resolution of symptoms.

II. Anticonvulsants

Anticonvulsants may be used as adjunctive therapy for neuropathic cancer pain, especially for patients with lancinating pain or those poorly responsive to opioid therapy.^{1,3,10,11,14} They may decrease opioid dose and associated side effects.¹

Gabapentin is effective in a variety of neuropathic pain syndromes, including neuropathic cancer pain.^{24,35-45} A study of patients with neuropathic cancer pain partially responsive to opioid therapy (n=22) showed that the addition of gabapentin decreased mean global pain score from 6.4 to 3.2.⁴³ Burning pain intensity decreased from 5.1 to 2.0 and episodes of shooting pain decreased in frequency from 7.2 to 2.2 episodes/day.

More recently, a multicentre, randomized, double-blind, placebo-controlled trial established the efficacy of gabapentin in neuropathic cancer pain.⁴⁴ The study involved 121 cancer patients with neuropathic pain that was partially controlled by systemic opioids. Patients were randomized to receive placebo or gabapentin (600 to 1,800 mg/day) for 10 days. Previous analgesics and adjuvant therapies were unchanged and one extra opioid dose per day was available as needed. Patients receiving gabapentin had significantly lower global pain scores (measured on a 0-10 numerical scale) than placebo-treated patients (4.6 vs 5.4, $p=0.025$). Gabapentin-treated patients also had less severe dysaesthesia (measured on a 0-10 numerical scale) than those receiving placebo (4.3 vs 5.2, $p=0.0077$).

Older anticonvulsants, such as phenytoin and carbamazepine, have also been used traditionally for analgesia.⁴⁵ However, their adverse effect profiles are less favourable than that of gabapentin,⁴⁶ and evidence supporting their efficacy in neuropathic cancer pain is lacking.

Other anticonvulsants have recently been developed for neuropathic pain treatment. Pregabalin is an analogue of gamma-aminobutyric acid and has analgesic, anticonvulsant and anxiolytic activity. Randomized, controlled, multicentre trials have demonstrated the efficacy of pregabalin in neuropathic pain syndromes, such as painful diabetic peripheral neuropathy and postherpetic neuralgia.^{47,48} Compared with gabapentin, pregabalin has more potent binding affinity for the active site of presynaptic calcium channels.⁴⁹ Pregabalin also has a more favourable pharmacokinetic profile than gabapentin, with analgesic efficacy demonstrated in some studies after the first day of treatment.^{48,49} Furthermore, pregabalin is effective with twice- or three-times daily dosing (total daily dose 150-600 mg), while gabapentin needs to be given in three divided doses (total daily dose 1,800-3,600 mg) and requires at least 9 days for titration to an effective dose.⁴⁹ Hence, pregabalin may also have a role in neuropathic cancer pain treatment.

Anticonvulsants for Post-treatment Neuropathic Pain

Gabapentin may also relieve neuropathic pain due to anticancer therapy. An open-label exploratory study involving cancer outpatients without active disease and with chronic, treatment-related pain (n=23) demonstrated a 4-week treatment with gabapentin 300 mg tid reduced pain intensity (measured by a 100-mm visual analogue scale [VAS]) from 60.93 to 30.20 mm ($p<0.01$) and increased the proportion of patients who achieved pain relief from 8.3% to 66.6% ($p<0.01$).²⁴

III. Antidepressants

Antidepressants have been the mainstay of therapy for many types of neuropathic pain. The number-needed-to-treat for antidepressants in neuropathic pain is between 1.7 and 4.7, depending on the neuropathic pain syndrome.⁵⁰ Antidepressants are also commonly recommended as adjunctive therapy for

neuropathic cancer pain, especially for patients with continuous dysaesthesia.^{1,3,10,11,14} These agents provide analgesia, potentiate the effect of opioids, and reduce depression and insomnia.^{12,51}

Although commonly used in practice, controlled trials evaluating the analgesic efficacy of tricyclic antidepressants in cancer patients report unconvincing results. However, limitations in study design might have contributed to incorrect interpretations. One randomized, controlled trial (n=184) found that short-term imipramine 10 or 25 mg tid, when used in combination with diclofenac (with or without codeine) in cancer patients with moderate-to-severe pain, had similar efficacy to placebo.⁵² Unlike other trials, however, patients were not concomitantly administered strong opioids. Furthermore, the final pain scores were assessed on day 4, which might have been too early to reflect the effect of imipramine.

Another 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.⁵³ However, this study was limited by low patient numbers and a relatively short washout period (2 weeks). A further study (n=20) showed a combination of antidepressants and anticonvulsants reduced neuropathic pain that was unresponsive to conventional analgesics, with maximum response occurring within 1 week.¹⁶

Antidepressants for Post-treatment Neuropathic Pain

Antidepressants may be effective for neuropathic pain due to anticancer treatment. A randomized, double-blind, placebo-controlled crossover trial (n=15) demonstrated amitriptyline effectively reduced neuropathic pain following treatment of breast cancer. However, adverse effects hindered its regular use.²⁵

Another study (n=13) showed maximum pain intensity was lower in patients treated with venlafaxine compared with placebo, and adverse effects from venlafaxine were similar to that from placebo.²⁶

IV. Anaesthetics and Antiarrhythmic Agents

Anaesthetics are often used as primary therapy for treatment of cancer-associated neuropathic pain, whereas some centres use them as second-line agents.¹⁷ However, there is limited evidence supporting their use for cancer pain. There are a few reports that subcutaneous infusion of lidocaine 10% improves pain refractory to systemic and spinal opiates in patients with terminal malignancy.⁵⁴ However, a systematic review reported that although intravenous lidocaine was effective for non-cancer-related neuropathic pain, it had no effect on cancer-related pain.⁵⁵

Oral mexiletine showed some efficacy in pain due to peripheral nerve damage, but not for central pain.⁵⁵ Furthermore, a randomized, double-blind, placebo-controlled trial (n=75) revealed oral mexiletine 600 mg/day reduced acute pain due to breast cancer surgery and analgesic requirements.⁵⁶ However, it did not affect chronic pain and the study did not specify the effect on neuropathic cancer pain.

The anaesthetic ketamine is an N-methyl-D-aspartate (NMDA) antagonist that has potent analgesic effects at subanaesthetic doses.⁴ Reviews indicate ketamine may reduce hypersensitivity in the dorsal horn and alleviate NMDA-related neuropathic pain, and has a synergistic effect with opioids in cancer pain patients who are unresponsive to high-dose morphine.^{4,57} However, because of its adverse effects, ketamine therapy should be instituted by experienced teams.¹³

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.^{7,12}

VI. Capsaicin

The primary role of capsaicin in neuropathic cancer pain is in postsurgical neuropathic pain. A study involving cancer patients with postsurgical neuropathic pain (n=99) showed 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 capsaicin as the more beneficial treatment (60% vs 18% for placebo, p=0.001).

Interventional Therapy

I. Neuraxial Drug Administration

Spinal analgesia effectively relieves refractory cancer pain and should be considered for patients with pain that is poorly responsive to conventional routes, and those with poor tolerance to systemic medications.^{7,58,59} 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.⁵⁹ A retrospective study (n=43) demonstrated intrathecal opioids initially reduced pain severity by 61.1% in patients with neuropathic cancer pain.¹⁸ However, pain reduction was

Appendix 1: Evidence-based Management of Neuropathic Cancer Pain

attenuated in the long term (11.1% median pain reduction).

Intraspinal clonidine may also be effective for neuropathic cancer pain. Eighty-five patients with severe cancer pain uncontrolled by opioids were randomized to receive epidural clonidine 30 µg/hour or placebo for 14 days, together with rescue epidural morphine.¹⁹ Pain was assessed by VAS, McGill Pain Questionnaire and dose of daily epidural morphine use. Success was defined as a decrease in either morphine use or VAS pain, with the alternative variable either decreasing or remaining constant. Successful analgesia was more common with epidural clonidine (45%) than with placebo (21%), and was particularly prominent in neuropathic pain patients (56% vs 5%). At the end of the treatment period, pain scores were lower in patients with neuropathic pain treated with clonidine than with placebo, whereas morphine use was unaffected.

Spinal administration of other anaesthetics may be effective as an adjunct to intrathecal opioids, but its efficacy on neuropathic cancer pain is anecdotal.⁶⁰⁻⁶²

II. 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.⁶³ It also improved pain severity and sleep in patients with diabetic neuropathic pain.⁶⁴ However, evidence to support its use in neuropathic cancer pain is lacking.

Spinal cord stimulation may be effective in a variety of neuropathic pain syndromes, including complex regional pain syndrome, postherpetic neuralgia and ischaemic pain associated with diabetic neuropathy.⁶⁵⁻⁶⁷ However, a systematic literature review showed that although spinal cord stimulation is beneficial in vasculopathic and postherpetic neuralgia, it has no clinical usefulness in cancer pain.⁶⁸ The review did not specify the nature of cancer pain involved.

III. Neural Blockade

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.²⁰⁻²² 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 due to poor response or tolerance.¹⁷ A clinical review further concluded that neurolytic sympathetic procedures for pancreatic and pelvic cancer may be useful for reducing pain when multiple pain mechanisms are involved.⁶⁹ However, literature on the use of neurolysis specifically for neuropathic cancer pain is scarce and suggests a limited role, with one review stating peripheral neurolytic blocks may be helpful in some cancer patients with peripheral neuropathies.²³

Undermanagement

Despite the presence of cancer pain guidelines, such as those from the World Health Organization (WHO), cancer pain is often undertreated. A large-scale study of patients with recurrent or metastatic cancer revealed that 42% of patients suffering from pain received inadequate analgesia.² This may be due to inadequate knowledge of pain management, poor pain assessment, reluctance to use analgesics and restrictive analgesic regulations.^{1,2}

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.¹ Other authors have 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.^{4,13} Therefore, these guidelines should be used judiciously.

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A complete list of references can be obtained upon request to the editor.