

Neuropathic pain in primary care

Koch K, MBChB

Private Practice General Practitioner, Freelance Medical Writer
Correspondence to: Karen Koch, e-mail: karenk@vodamail.co.za

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Abstract

Pain is the most common reason why patients seek medical help. Persistent and unrelieved pain can frustrate both the sufferer and the physician trying to alleviate it. Relief from chronic pain may be particularly difficult to achieve and can be fraught with misconceptions. Neuropathic pain is widely recognised as one of the most difficult pain syndromes to treat and presents a significant challenge for pain clinicians and general practitioners. Often, patients have poor pain resolution. It is important that patients with any chronic pain are identified and managed appropriately according to their distinct treatment needs.

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Introduction

Neuropathic pain is defined as “pain that is initiated or caused by a primary lesion or dysfunction in the nervous system”.¹ Chronic neuropathic pain is relatively common, affecting 8% of people in the general population.² Regardless of the initiating condition, neuropathic pain is widely recognised as one of the most difficult pain syndromes to treat. It presents a significant challenge to clinicians as it does not always respond to conventional analgesic therapies.^{3,4}

What causes neuropathic pain?

While nociceptive pain results from a known or obvious source, e.g. trauma, cancer metastasis and ischaemia, and the source is often easy to identify, neuropathic pain may occur in the absence of an identifiable precipitating cause. A definitive underlying diagnosis is found in less than 40% of patients with peripheral neuropathy and neuropathic pain.⁵

Neuropathic pain is a common complication of cancer, diabetes mellitus, degenerative spine disease, infection with human immunodeficiency virus and other infectious diseases, and has a profound effect on quality of life.⁶

The disorder can be caused by compression, transection, infiltration, ischaemia or metabolic injury to neuronal cell bodies. Neuropathic pain may be classified as either peripheral or central in origin.⁷ Examples of each type are outlined in Table I.⁷

Table I: Examples of types of neuropathic pain

Some common causes of neuropathic pain ⁷	
Peripheral nerve lesion or dysfunction	Central nerve lesion or dysfunction
Painful diabetic neuropathy	Central post-stroke pain
Postherpetic neuralgia	Multiple sclerosis pain
Postsurgical pain (including post-mastectomy and phantom limb pain)	Spinal cord injury pain
Complex regional pain syndrome	
Trigeminal neuralgia	
Chemotherapy-induced neuropathy	
Neuropathy secondary to tumour infiltration	

Neuropathic pain utilises the same pain pathways as nociceptive pain signals. Information regarding intensity, quality and location of pain is conveyed to the sensory cortex from the somatosensory thalamus. The central nervous system utilises descending inhibitory pathways via the dorsolateral fasciculus (Lissauer's tract) of the spinal cord and the periaqueductal grey matter to modulate transmission of nociceptive stimuli.^{8,9} Nociceptive pain stimulates a protective mechanism, e.g. removing a hand from the hot plate, while neuropathic pain signals no imminent danger.¹⁰

The operative difference is that neuropathic pain represents a delayed, ongoing response to damage that is no longer acute, which continues to be expressed as painful sensations. Sensory neurons that are damaged by injury, disease or drugs produce spontaneous discharges that lead

to sustained levels of excitability. These ectopic discharges begin to “cross talk” with adjacent uninjured nerve fibres, resulting in amplification of the pain impulse (peripheral sensitisation).¹⁰

This hyperexcitability leads to increased transmitter release, causing increased response by spinal cord neurons (central sensitisation). The process, known as “windup,” accounts for the fact that the level of perceived pain is far greater than what is expected based on what can be observed.^{11,12}

Identifying neuropathic pain

Multiple symptoms can help lead to a diagnosis of neuropathic pain.⁷ Neuropathic pain sufferers complain of numbness, burning or tingling, or a combination. They describe electric shock-like, prickly, or pins-and-needles-type sensations. Electric shocks, burning, tingling, cold, prickling and itching are the most commonly used phrases to describe neuropathic pain. Table II lists the symptoms and signs that may be present in neuropathic pain.¹³

Table II: The signs and symptoms of neuropathic pain¹³

Symptom or sign	Description
Allodynia	Pain due to nonnoxious stimuli (clothing and light touch) when applied to the affected area. It may be mechanical (caused by light pressure), dynamic (caused by nonpainful movement of a stimulus), or thermal (caused by a nonpainful warm or cool stimulus)
Anaesthesia	Loss of normal sensation to the affected region
Dysesthaesia	Spontaneous or evoked unpleasant abnormal sensations
Hyperalgesia	Exaggerated response to a mildly noxious stimulus applied to the affected region
Hyperpathia	Delayed and explosive response to a noxious stimulus applied to the affected region
Hypoesthesia	Reduction of normal sensation to the affected region
Paresthaesias	Nonpainful spontaneous abnormal sensations
Phantom pain	Pain from a specific site that no longer exists, e.g. an amputated limb, or where there is no current injury
Referred pain	Occurs in a region remote from the source

The Neuropathy Pain Scale is a specifically designed 10-question assessment which helps practitioners identify neuropathic pain.¹⁴

In particular, high scoring for sharp, sensitive, cold and itchy characteristics commonly correlates with a diagnosis of neuropathic, rather than nociceptive, pain.¹⁴

Management of neuropathic pain

Neuropathic pain tends to exhibit a relatively poor response to traditional analgesics.^{8,15} No cure for neuropathy exists.

However, palliation of pain, restoration of therapeutic sleep and maintenance of function and improvement in overall quality of life remain the mainstay of treatment. Treatment with anticonvulsants, such as carbamazepine and gabapentin, or antidepressants (particularly amitriptyline), can be effective in treating neuropathic pain.^{16,17}

Adequate treatment trials demand a long-term commitment from both the patient and the physician.¹⁸ Adherence to the prescribed agent and adequate time for the trial are needed for any regimen to be effective. As with many difficult medical problems, a multidisciplinary approach to treatment is often the most successful. A multidisciplinary pain relief team includes primary care physicians, neurologists, pain specialists such as anaesthesiologists or neurosurgeons, psychiatrists, psychologists, pastoral counsellors, advanced practice nurses and clinical pharmacologists. As always, the most important member of this team is the patient.

Medications that are used to treat neuropathic pain include over-the-counter analgesics, anticonvulsants, tricyclic antidepressants (TCAs), topical anaesthetic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), antiarrhythmics and opioids.^{7,15,18} This varied armamentarium reflects the heterogeneity of the patient group and the different pathophysiological mechanisms that are postulated to produce neuropathic pain.

Antidepressants

TCAs are considered to be the first-line treatment for neuropathic pain, provided patients do not have any known contraindications.¹⁹ They are limited by a slow onset of action (analgesia in days to weeks), anticholinergic side-effects (a dry mouth, blurred vision, confusion or sedation and urinary retention), and potential cardiac toxicity. Amitriptyline hydrochloride is the most extensively studied of the TCAs. It is given in oral doses of 10-25 mg at bedtime. This dose can be slowly titrated with escalating doses every 4-7 days. Frail and elderly patients may be unable to tolerate therapeutic doses because of the sedation.¹⁹

The advent of selective serotonin reuptake inhibitors gave hope that they could be used to treat chronic pain without the concerns of cardiac toxicity and anticholinergic side-effects. However, results have been disappointing.¹⁰ Duloxetine is recommended when patients cannot tolerate TCAs or TCAs have yielded an inadequate response. The dose should be started at 60 mg daily and titrated up to 120 mg daily as needed. A trial of therapy for up to four weeks is recommended.¹⁰

Patients with neuropathic pain are prone to depression, drug dependency and insomnia. Interrupted sleep is one of the most difficult problems experienced by patients with neuropathy. Antidepressants and sedative-hypnotic

medications may be prescribed as important adjunctive therapy for neuropathy.¹⁰

Anticonvulsants

Anticonvulsants have been used for several years in the management of neuropathic pain. They are considered to be second-line agents to antidepressants in the management of neuropathic pain.

Gabapentin is structurally related to γ -aminobutyric acid, a pain-modulating neurotransmitter that readily crosses the blood-brain barrier. It has been studied for the treatment of patients with diabetic peripheral neuropathy. Pain relief efficacy is similar to that of tricyclic antidepressants, except for a shorter onset of action. Gabapentin is often needed in relatively high doses to achieve pain relief which can result in side-effects such as dizziness and somnolence. An eight-week trial is recommended.²⁰

Pregabalin is recommended when gabapentin is ineffective. Usually a four- to six-week trial is recommended.¹⁰

Topical anaesthetic agents

Patients with localised regions of peripheral neuropathy may respond well to topical lidocaine hydrochloride 5% patches, especially if the region of pain is relatively small and circumscribed. Studies have demonstrated the efficacy of topical lidocaine. It is safe, easily administered and has minimal side-effects.^{21,22} Unfortunately, these high-dose patches are not available in South Africa.

Anti-inflammatory agents

The usefulness of NSAIDs, such as aspirin and ibuprofen, for neuropathic pain is limited. Use of NSAIDs should be discouraged because of the adverse effects of these drugs on renal function. The cyclo-oxygenase-2 inhibitors have been under scrutiny for causing adverse cardiovascular events and cannot be recommended for the long-term administration that is needed to treat patients with neuropathic pain syndromes.¹⁰

Opioid analgesics

In response to severe or persistent pain, interneurons in the dorsal horn release endogenous opioids that work to reduce perceived pain. These endogenous substances (enkephalins, endorphins and dynorphins) play a major role in the mechanism of pain reduction and modulation by preventing transmission of pain signals to higher centres. Exogenously administered opioids mimic the effect of enkephalin and dynorphin at mu-type opioid receptors which occur throughout the brain and spinal cord. This mechanism accounts for the efficacy of opioid analgesics in neuropathic pain syndromes.²³

Tramadol hydrochloride, a semisynthetic opioid analgesic, may also affect neuropathic pain by low-affinity binding to mu receptors. It may also do so by weakly inhibiting norepinephrine and serotonin reuptake, mirroring the mechanism of action of both opioids and TCAs. One trial suggests that tramadol may be better tolerated than TCAs in some individuals with diabetic peripheral neuropathy or other neuropathic pain syndromes.²⁴

Because of concerns about tolerance, abuse and addiction, the use of opioids in treating nonmalignant pain was formerly considered to be controversial. However, in recent years, considerable research has supported the use of these agents. Neuropathic pain is now treated with opioids commonly and effectively.^{15,19,25-27}

Combined therapy

Clinical experience supports the use of more than one agent to treat patients with refractory neuropathic pain. Because there may be several physiological mechanisms that cause pain, the use of more than one type of medication may be necessary.

While monotherapy may be desirable, both for ease of administration and the reduction of potential side-effects, this approach may not achieve satisfactory pain relief. The strategy of using two or more agents at lower doses to achieve synergistic pain efficacy is an effective one.^{19,28,29} The most widely studied combination is gabapentin used with morphine to manage neuropathic pain.¹⁹ It was found to be more effective than either agent used alone, suggesting that combination treatment strategies offer synergistic pain control.

Managing neuropathic pain

It is particularly important that patients with neuropathic pain are identified in primary care and managed appropriately according to their individual treatment needs. Patients with neuropathic pain often don't respond to commonly used analgesics and require ongoing treatment that targets the underlying mechanisms that are responsible for the sensitisation and the experience of pain.

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