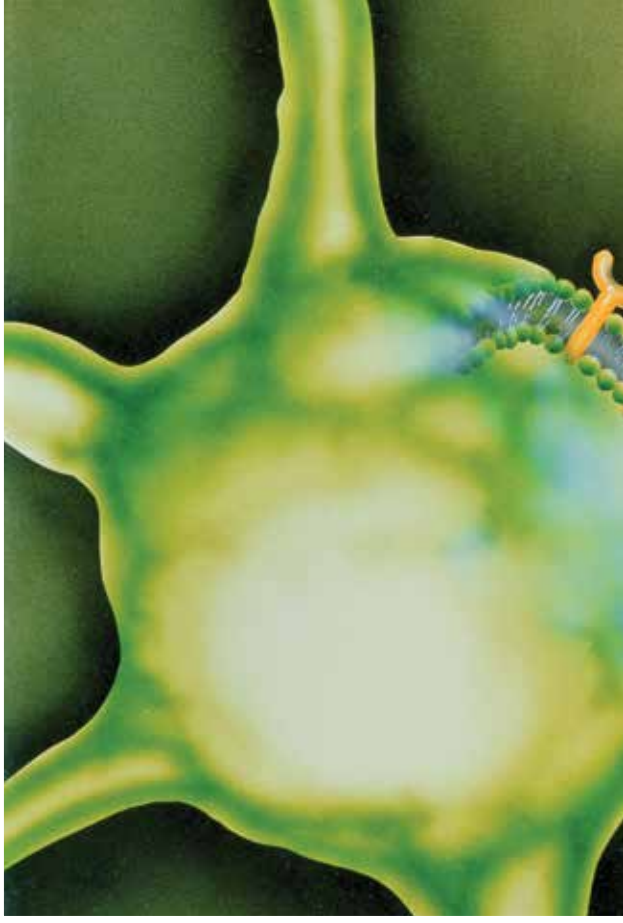
Pharmacological management of neuropathic pain



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Neuropathic pain is caused by several conditions including trigeminal neuralgia and diabetic neuropathy. Management should be individualised to each patient, finding a drug and dose that gives each person the best relief from their pain.

Key points

- **Of patients with chronic pain, 10% have a neuropathic component.**
- **Careful assessment of affected patients is pivotal to a correct diagnosis.**
- **Management of patients with neuropathic pain is always holistic.**
- **Medications only reduce pain severity and only in half of patients treated for neuropathic pain.**
- **Patients with neuropathic pain should be referred to a physician in pain medicine if uncertainty pertains to observed outcomes.**

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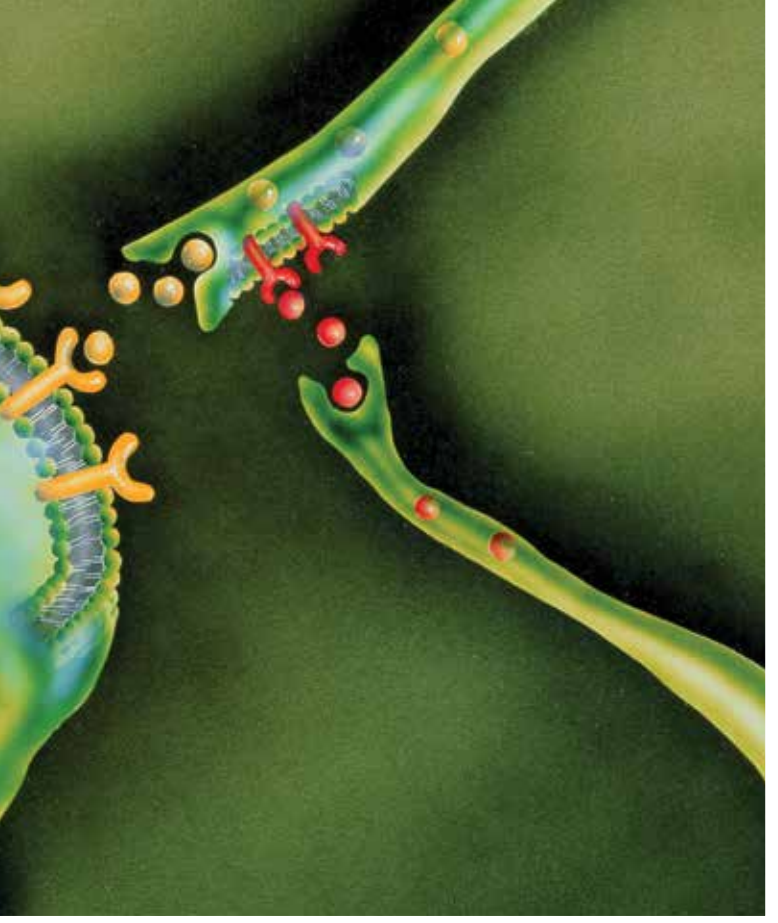
Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system.[1] The best estimate of population prevalence of pain with neuropathic characteristics is between 7% and 10% but a wide range of values has been cited.[2] Nevertheless, the diagnosis can often be overlooked unless the patient is carefully assessed.

The most common conditions that cause neuropathic pain are compressive nerve injuries, such as carpal tunnel syndrome, painful diabetic neuropathy, postherpetic neuralgia and trigeminal neuralgia. Collectively, genetic causes are also common but remain poorly characterised. Easily missed diagnoses include erythromelalgia (relatively common) and Fabry disease (rare). Examples of causes of peripheral neuropathic pain are direct nerve injury including surgical trauma and complex regional pain syndrome (CRPS) type II, diabetes and other causes of painful peripheral neuropathy, painful radiculopathy, brachial plexus injury and phantom limb pain. Causes of central neuropathic pain include spinal cord injury, syringomyelia, stroke, Parkinson's disease and multiple sclerosis. Other categories of pain may have a neuropathic component but are poorly understood, such as CRPS type I and fibromyalgia, and are not considered here.

Screening tools are available to assess if a patient's pain is neuropathic. Two examples of these screening tools are the Douleur Neuropathique 4 (DN4) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), which record data on both spontaneous and evoked pain. These screening tools have limited sensitivity and specificity and their use is best confined to clinical research; however, they may be useful as an aide memoire.

An approach to classifying neuropathic pain as definite, probable or unconfirmed is shown in the flowchart.[3] Although still a subject



of debate, this represents an advance in recent thinking on this enigmatic condition where it is possible to have pain in a region of the body that is insensate. If the pain cannot be determined to be definite neuropathic pain using the algorithm, referral of the patient to a pain specialist must be considered.

It should be remembered that spontaneous and evoked pain may spread outside the recognised anatomical boundaries for nerves, transmission pathways and receptor fields, both central and peripheral. However, clinical examination determines that there are abnormalities within those boundaries in cases of definitive neuropathic pain. The exceptions are trigeminal neuralgia and glossopharyngeal neuralgia, which are not associated with altered sensation during clinical examination, although research studies have shown subtle deficits.

Several interacting mechanisms may be responsible for neuropathic pain. Once established, pain prolongation is usually maintained by non-noxious sensory input.[4] Despite more than a decade of research, there are no treatments targeted specifically to pain aetiology, mechanism or individual characteristics of the pain experience, although slow progress is being made.

Treatment of neuropathic pain

The management of patients with neuropathic pain is difficult. Surgery is directed at any underlying cause where indicated. Although medical therapy applied from a biopsychosocial perspective may be only partially effective, it provides the preferred avenue for the long-term treatment of pain in most cases.

Most drug trials have been undertaken over three months in patients with the common causes of peripheral neuropathic pain and the results extrapolated to longer time frames and other conditions. A 50% reduction in the level of pain is considered an appropriate positive clinically relevant end point, although 30% is sometimes accepted. For a pain treatment to be considered effective, the numbers needed to treat (NNT) for one patient to achieve this end point should be less than five. Comparisons can be made between drugs by looking at their NNT, but caution is advised as outcomes may be affected by methodological factors.[5] The Table summarises recent data.[5,6] There are limited studies of drug combinations or direct comparative trials of different drug classes but this practice has been widely adopted in clinical practice.

As with all patients experiencing pain, attention must be directed towards acute and persistent disturbances in mood state and to the patient belief systems and environment. Nonpharmacological and complementary treatments may be useful conjointly in reducing and managing individual patients. If the patient is not making progress, even despite individual disciplinary input, referral to a multidisciplinary pain management clinic may be helpful. Alternative treatments such as local nerve block and ablative procedures (e.g. radiofrequency lesions), intrathecal drug treatment, implantable peripheral nerve, spinal cord and motor cortex stimulators, and cognitive behavioural pain management programs may then be considered for selected conditions if the patient is psychologically stable.[7] Detailed reviews of the pharmacological management of patients with neuropathic pain are recommended for practitioners who manage complex cases.[7-9] As always, a prescriber needs to be cognisant of adverse events attributed to these medications over time as well as after initiation; they are not all listed here.

Simple analgesics

Neuropathic pain is usually refractory to simple analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs). Pain due to nociceptor stimulation (e.g. inflammatory and degenerative conditions) in patients with neuropathic pain will, however, respond to these medications used at standard doses but there is no direct effect on the underlying neuropathic pain.

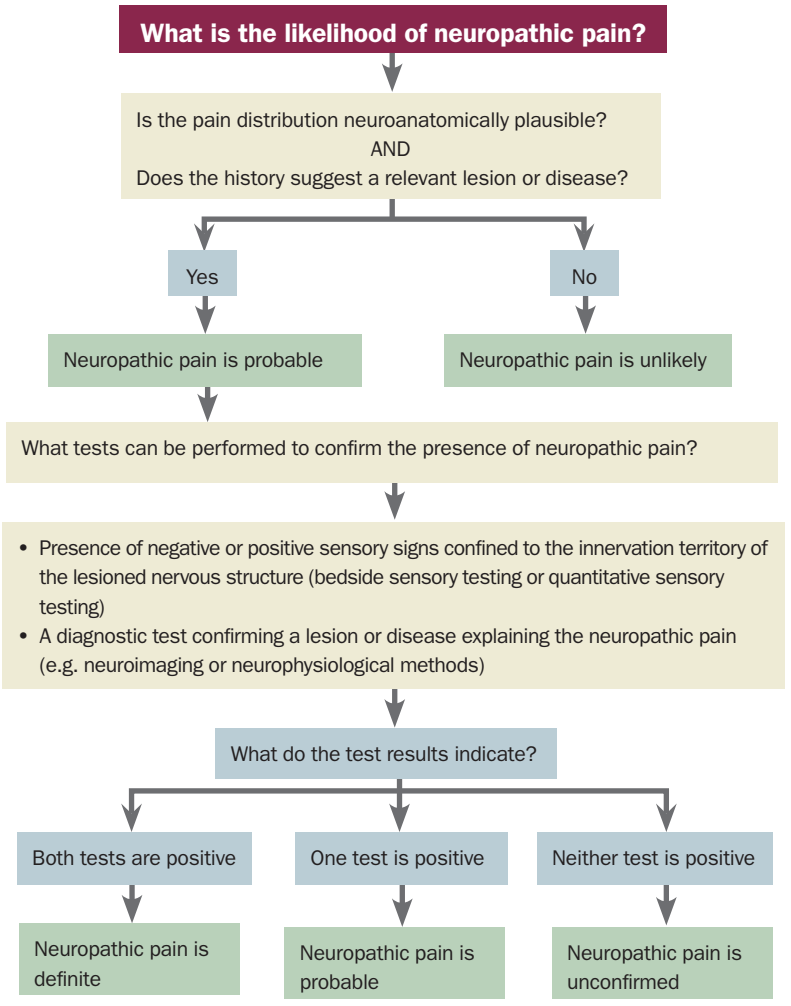
Analgesic adjuvants

The treatment of patients with neuropathic pain usually requires the use of analgesic adjuvants such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs) and/or antiepileptic drugs. TCAs, SSRIs and SNRIs are all used off label for the treatment of patients with neuropathic pain. Use of N-methyl-D-aspartate (NMDA)-receptor antagonists, local anaesthetics and capsaicin 8% generally requires additional input from a pain medicine physician, and a compounding pharmacist for capsaicin. Most drugs are used orally, but local anaesthetics (e.g. lignocaine) and NMDA-receptor antagonists (e.g. ketamine) can be administered parenterally or topically. Cure is not anticipated, only pain attenuation.

Antidepressant drugs

TCAs appear to relieve pain independently of their mood-altering effect, in part by inhibition of nociceptive transmission due to

Classifying the certainty with which neuropathic pain can be diagnosed[3]



Modified from: Haanpää M, Treede RD. Diagnosis and classification of neuropathic pain. Pain; Clinical Updates 2010; XVIII (7): 1-6.[3]

inhibition of synaptic noradrenaline and serotonin reuptake, although they have other actions (e.g. local anaesthetic, anticholinergic, antihistamine and gamma-aminobutyric acid [GABA] activity) that may be relevant. Amitriptyline is the TCA most commonly used. If amitriptyline causes unacceptable adverse effects, an alternative such as nortriptyline or doxepin can be used. TCA use is rarely precluded as in, for example, active ischaemic cardiac disease, but adverse effects are common, particularly drowsiness and cognitive and anticholinergic effects, especially in older people. Dry mouth is a universal side effect.

Doses of TCAs for treating patients with neuropathic pain are smaller than those for treating patients with depression, and a trial of at least four to six weeks is required. Amitriptyline 5, 10 or 25 mg orally is used at night, usually one hour before going to bed, and doses are increased every seven days to a usual maximum dose of 75 mg, and occasionally 100 mg daily.

If TCAs are prescribed, caution should be exercised if the patient is also taking drugs that have serotonergic activity or otherwise interact with TCAs, such as SSRIs, SNRIs, monoamine oxidase inhibitors (used concomitantly for depression) and tramadol. TCAs have not been shown to be of benefit in patients with pain from a spinal cord injury, HIV neuropathy, chemotherapy-induced neuropathy or phantom limb pain.

Selective noradrenaline reuptake inhibitors

The SNRI duloxetine is on the PBS for the treatment of patients with depression and not pain, despite the positive trials in patients with painful diabetic neuropathy; however, it is widely used as most affected patients have mood disturbance requiring concomitant treatment. The dose used is 30 mg daily for four weeks, increasing to 60 mg daily if needed, and it is taken with food to attenuate any epigastric discomfort. Timing of the dose can be varied from patient to patient. Venlafaxine is generally thought to be less effective.

Antiepileptic drugs

Antiepileptic drugs decrease the excitability of neurones at the spinal and brain levels and may work by increasing the effectiveness of the other major inhibitory network involving gamma-aminobutyric acid (GABA). Gabapentin and pregabalin modify the action of voltage-gated calcium channels of primary afferents and thereby interfere with the release of substance P, noradrenaline and the excitatory amino acid neurotransmitter glutamate. There is no direct correlation between the plasma reference range of antiepileptic drugs recommended in the treatment of patients with epilepsy and their efficacy in the treatment of patients with neuropathic pain. They are generally used to tolerance.

Large studies have shown that gabapentin and pregabalin are of benefit in the treatment of patients with pain associated with postherpetic neuralgia and diabetic neuropathy, and two trials have shown benefit for those with central neuropathic pain from spinal cord injury. Failure to respond to either gabapentin or pregabalin does not predict failure to the other drug; the tolerability and efficacy of the two drugs may be different in individual patients. Gabapentin is used at a daily oral dose of 100 to 300 mg, increasing as tolerated and according to response every four days from once daily to three times daily, to a usual maximum daily dose of 3600 mg (higher if tolerated). Pregabalin is started at a dose of 75 mg orally, daily initially, increasing to twice daily after two or three days and then more slowly up to 300 mg twice daily (the maximum dose used in the trials) or

even higher. Pregabalin is available in units of 25 mg for patients with renal failure and can be started at this dose in otherwise frail or elderly patients with normal renal function if preferred. Cases of addiction to gabapentinoids are beginning to appear in the literature but mostly in patients with prior opioid abuse.

Sodium valproate, phenytoin, carbamazepine, oxcarbazepine, levetiracetam, lamotrigine, lacosamide, clonazepam and topiramate have been used to treat patients with neuropathic pain, but trial evidence for benefit is absent or very limited (e.g. one positive and one negative trial) so meta-analyses cannot be performed. None of these drugs are approved for this purpose; however, individual patients may benefit from an add-on approach to treatment on occasion.

Table. Numbers needed to treat to achieve 50% pain reduction in patients with neuropathic pain*[5,6]

Medication	Neuropathy†	Postherpetic neuralgia	Peripheral nerve injury	Spinal cord injury/ stroke
Tricyclic antidepressants	2.1	2.8	2.5	4
SSRI	6.8	id	id	id
SNRI	5	id	id	id
Pregabalin	4.5	4.2	id	5.6
Gabapentin	5.9	4.3	id	id
Sodium valproate	id	2.1	id	ns
Tramadol	4.9	4.8	id	ns
Strong opioids	2.6	2.6	5.1	id
Capsaicin 8%	5.8	7	id	id

Abbreviations: id = insufficient data/not done; ns = not significant; SNRI = selective noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
* Meta-analyses of trials from 2010 to 2014 in respect of number needed to treat for 50% pain relief.[5,6]
† Mostly painful diabetic neuropathy.
Insufficient data available for carbamazepine, clonazepam, lacosamide, lamotrigine, levetiracetam, 5% lignocaine patch, oxcarbazepine, phenytoin and topiramate.

Choice of analgesic adjuvant

The choice of analgesic adjuvant is largely dependent on consideration of efficacy, adverse effects and cost. The best available evidence still supports the current guidelines of using TCAs (and SNRIs where indicated) and gabapentinoids as first-line therapy and opioids as second-line therapy.

The most striking example of selective efficacy is that demonstrated by carbamazepine for patients with trigeminal or glossopharyngeal neuralgia. There are no substantive trials of benefit of this medication in patients with other causes of neuropathic pain. The medication is used to tolerance after being introduced in small doses in these two conditions, often as low as 50 mg daily or twice daily in frail elderly people, although benefit usually requires a minimum dose of 250 mg twice daily. On the other hand, the most frequently used second-line drug for patients with trigeminal neuralgia, before considering a neurosurgical option, is now pregabalin (off-label use), where no such selectivity applies.

With the changing demographics of the country, it is worth noting the occurrence of Stevens-Johnson syndrome in Asian patients, particularly those of Han Chinese origin, who carry the HLA-B*1502 haplotype (up to 10%). The presence of this haplotype can be determined locally but testing may be expensive for the patient and the result takes about a week to 10 days to come back from the laboratory.

Other clinical indications based on the drug side effect profile (e.g. need for sedation) or contraindications (e.g. sedation, prostatism, cognitive impairment, potential for weight gain) may also influence the choice of drug. Cognitive side effects occur with all these medications at high doses in most patients. Remembering the occurrence of non-pitting ankle swelling with the use of gabapentinoids can reduce needless worry for doctor and patient.

Opioids

Tramadol, classified as a weak opioid, has serotonergic and noradrenergic effects and is therefore worth considering in patients with neuropathic pain before a trial of a strong opioid. Other weak opioids (e.g. codeine) can be trialled but evidence of benefit is limited.

Patients with neuropathic pain are less responsive to strong opioids than those with nociceptive pain. Trials have mostly been performed in patients with postherpetic neuralgia or painful diabetic neuropathy; patients with central neuropathic pain appear to respond less well. Higher doses are generally required and side effects are therefore more likely to be bothersome; trial doses average from 100 to 150 mg morphine equivalent. Titration with a short-acting opioid with transfer to a long-acting form is the usual practice, although it has not been well validated.

Extensive discussion with the patient is needed, preferably using an opioid risk tool, before commencing treatment with opioids and, given the chronic nature of neuropathic pain, an initial written agreement of the terms for opioid use as well as frequent monitoring of drug use is mandatory. Regulatory conditions vary somewhat between states. As for use in patients with nociceptive pain, if there is initial benefit followed by an escalating dose requirement, or if the maximum dose of morphine equivalent exceeds 100 to 160 mg daily (it varies between states), advice from a pain physician should be obtained. This, together with the potential for addiction, make opioids a less attractive

option than analgesic adjuvants over the long term. In longer trials, most patients have ceased opioids after six to 12 months.

Evidence is growing that misuse of prescribed opioids in patients with nonmalignant pain is increasing with rising numbers of deaths from overuse. Likely adverse effects of chronic opioid use, such as osteoporosis, dental caries, endocrine effects and possibly immune suppression, should also be considered.

Local anaesthetics

Injection of local anaesthetics are mostly used for diagnostic purposes in patients with unusual sites of presumed neuropathic pain. The beneficial effect is usually only two to four hours; however, on rare occasions this may last for up to a few months. Topical local anaesthetic application repeated several times a day has also been used for its more long-lasting effect but the methods for application and maintenance of contact have generally been unsatisfactory and use has been limited. More recently 5% lignocaine patches have become more readily available and are proving useful in patients with superficial painful neuropathic conditions, particularly postherpetic neuralgia and painful peripheral neuropathy (where the expense is likely to be high), and its use in treating patients with allodynia is widespread. Skin irritation may preclude its use; however, allergies to local anaesthetics are rare.

Treatment of refractory neuropathic pain

It may be necessary to use drugs from more than one class concurrently (e.g. a TCA, SNRI, combined antiepileptic drugs and opioids) to treat patients with refractory neuropathic pain. However, the evidence for benefit of combination therapy is limited and the best strategy for introducing two medications, let alone more than two, has still to be determined.[10] For example, do you use one medication to tolerance and then introduce a second drug? Or reduce or cease the dose of the first before introducing the second? Or initiate both together? Combination trials rarely demonstrate improvements in primary outcomes related to pain measures, but often show positive benefits in secondary outcomes such as sleep habit and mobility, suggesting the possibility of improvements in occasional individuals using this approach.

Advice from a pain physician, pain clinic or a palliative care specialist is strongly recommended before changing the treatment plan in a patient who is already known to have refractory neuropathic pain. A patient with severe refractory neuropathic pain may be trialled with the NMDA-receptor antagonist ketamine in an inpatient setting, often over several days. The side effects may be alarming, including severe hallucinations, but the outcome for reducing pain, at least in the short term and occasionally over a prolonged period, make it an attractive option in some circumstances. Responsive patients may then be trialled on sublingual, oral or intranasal ketamine for breakthrough pain, if available; however, trial evidence of benefit remains limited and its use is better undertaken by pain physicians.

Topical capsaicin in concentrations of 0.025% or 0.075% has been used to treat patients with refractory postherpetic neuralgia and painful polyneuropathy (including diabetic neuropathy) but is now used rarely. A much higher concentration of capsaicin (8%) can be used but often causes severe burning pain requiring prophylactic local anaesthetic application. The interval between doses is three months. The long-term effects of this dose of capsaicin on spinal cord mechanisms from retrograde transport are as yet unknown.

Cannabinoids and local intradermal injections of botulinum toxin have been trialled with positive outcomes but there is limited experience in Australia.[11] Morphine and local anaesthetics, as well as off-label baclofen and clonidine, may be administered using an implantable intrathecal infusion device by pain specialists experienced in its use.

Conclusion

Neuropathic pain is more common than previously recognised. The key to the management of affected patients is assessment, by history and neurological examination of both large and small fibre function. Confirmation by an appropriate investigation is preferred but may not be possible in some situations. Options for treatment always need discussion with the patient because of the limitations to treatment benefits and the likelihood of adverse effects. Treatment should be initiated at a low dose and escalated slowly if at all possible, and outcomes monitored. Patients should be referred if either you, the GP, or the patient have unsatisfied expectations. **PMT**

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COMPETING INTERESTS: Professor Helme has received honoraria from Pfizer (Australia).