



# Drug treatment of neuropathic pain

Robert D. Helme, Professor, Department of Medicine, Royal Melbourne Hospital, University of Melbourne, and Director, Department of Neurology, Western Health, Melbourne

## Summary

**The distress evident in many patients with neuropathic pain demands a trial of drug treatment. Evidence for satisfactory outcomes is limited so patients must be fully informed of the likely benefits and adverse effects of any trial. Antidepressants, anticonvulsants and opioids are the main drugs used to treat neuropathic pain. Management by a multidisciplinary pain clinic should be considered for patients with chronic, severe and disabling neuropathic pain.**

Key words: anticonvulsants, antidepressant drugs, opioids.

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## Introduction

Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system. One example is the phantom limb pain patients feel after amputation, but there are many possible causes (Table 1). The pain may be spontaneous, stimulus-evoked, or a combination of both. Its characteristics are often different from those of other types of pain, such as the nociceptive pain experienced after an injury.

In neuropathic pain the central neurons are sensitised, so that they fire spontaneously, or abnormally. If this sensitisation persists the pain becomes chronic and is often difficult to treat.

## Clinical evaluation

Doctors are familiar with taking a history of spontaneous pain to establish its location, temporal pattern, quality, severity, exacerbating and relieving factors. In neuropathic pain this approach needs to include other components:

- cognitive (that is, psychological determinants of pain such as fear, avoidance and catastrophising)
- affective (for example, anxiety, depression, frustration, anger, demoralisation)
- functional (for example, the impact of pain on activities and quality of life).

There are considerable overlaps in the pain descriptors between nociceptive and neuropathic pain. Some patients may have nociceptive and neuropathic pain. Clues to a neuropathic origin are its continuous nature (as opposed to movement-induced pain), burning and shooting qualities. There are also associated

symptoms (derived from irritation to non-noxious afferent neurons) such as numbness, dysaesthesia and formication in anatomically recognised patterns.

Important components of the assessment are the examination of the patient for evidence of abnormal stimulus-evoked pain<sup>1</sup> (see box), usually indicating central sensitisation, and routine neurological examination for sensory loss, particularly warm and cold sensibility, in recognisable anatomic patterns. The most confusing element is the extension of areas of stimulus-evoked pain beyond the anatomical boundary of the area receiving the stimulus. This occurs because central sensitisation does not respect these boundaries.

Table 1

### Common causes of neuropathic pain

Peripheral	Central
Trauma blunt trauma (5%) radiculopathy iatrogenic (surgery)	Stroke (8%)
Ischaemia	Multiple sclerosis (58%)
Entrapment	Spinal cord injury (50%)
Polyneuropathy hereditary metabolic (diabetes 11%) toxic immune infections paraneoplastic nutritional	Syringomyelia/bulbia (75%)
Stump and phantom pain	
Post-herpetic neuralgia	
Neuralgias trigeminal glossopharyngeal occipital	
Neoplastic tumour invasion radiation surgery chemotherapy	

The percentages are the reported proportions of patients with each condition who have neuropathic pain. For example, 11% of patients with diabetes have neuropathic pain.

### Sensory abnormalities in neuropathic pain<sup>1</sup>

Hypoaesthesia	– reduced touch sensation
Hypoalgesia	– reduced response to painful stimuli
Paraesthesia	– tingling sensation
Hyperalgesia	– increased response to painful stimuli
Allodynia	– pain due to a stimulus which does not normally produce pain
Hyperpathia	– an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. (This often explosive reaction is associated with continuing pain after cessation of the stimulus.)
Dysaesthesia	– an unpleasant abnormal sensation, whether spontaneous or evoked

The investigations of neuropathic pain vary according to the suspected cause of each syndrome. A cause should be sought in each case, and treatment of that cause may contribute to alleviation of symptoms and retard progression of the condition. For example, irritation caused by a prosthesis may be contributing to a patient's pain following amputation.

### Mechanisms of neuropathic pain

Both peripheral and central neuropathic pain syndromes rely on sensitisation of neurons in central pathways normally associated with the transmission of noxious stimuli. These pathways are the dorsal horn of the spinal cord, the spinothalamic tract (for somatic structures) and dorsal columns (for viscera), the thalamus, and the sensorimotor, limbic, prefrontal and insula cortex.

The sensitisation of neurons is characterised by increased background activity, a lowered threshold for activation (for example, by non-noxious stimuli), and the spread of receptor fields (increased firing of spatially diverse neurons ensuring larger areas of the body are represented in the conscious recognition of pain). Sensitisation is usually associated with partial denervation plus stimulation from continuously active afferent input (peripheral or central) which depends on activation of axonal sodium channels. Pain in the presence of complete deafferentation is rare, but much feared because of its lack of response to treatment.

The sensitisation of nociceptive neurons is the result of increased activity in excitatory pathways where substance P, excitatory neurotransmitters and adenosine triphosphate act via voltage-gated calcium channels and/or diminished activity in inhibitory pathways via gamma-aminobutyric acid (GABA) and glycine.

The most difficult chronic neuropathic pain syndromes to treat are associated with the irreversible loss of neurons. Mostly, this is by apoptosis initiated through both intrinsic calcium modulated systems in neurons, or by extrinsic inflammatory processes. This has led to the concept of chronic pain as an

(irreversible) disease within the nervous system. The implication is that neuropathic pain should be treated early in the course of its development to prevent it becoming chronic.

### Treatment

Non-drug treatments can help to control the patient's pain. A multidisciplinary approach may be required.

Current drug treatments are focused on dampening the neuronal input to consciousness by suppressing axonal function (for example sodium channel blockade) or interfering with neurotransmission (blockade of excitatory and inhibitory neurotransmitters and modulators). This approach is likely to be greatly modified over the next few years as the biology underlying these processes is better understood.

There are significant weaknesses in the trials that underpin current treatments for neuropathic pain. Large studies have been undertaken predominantly in patients with pain from diabetic neuropathy and post-herpetic neuralgia. The results of these studies are then extrapolated to other neuropathic pain states. When one considers that a successful outcome is deemed to be a 50% reduction in pain in 50% of patients, it is easy to appreciate we have a long way to go before we have highly effective treatments for neuropathic pain.

Unfortunately, the cost of trials is high, and they are generally only undertaken by drug companies. This limits the likelihood of 'head to head' trials and trials of drug combinations.<sup>2</sup> This means comparisons between drugs and drug classes must depend on analysis of numbers needed to treat and numbers needed to harm, despite criticisms of this methodology. These comparisons generally favour tricyclic antidepressants over anticonvulsants and opioids.<sup>3</sup>

Neuropathic pain is likely to be an ongoing complaint. A trial of treatment in an individual patient can therefore be planned. Due consideration is given to selection of measures of pain, activity, mood and adverse effects, in agreement with the patient before and after an agreed trial period. One drug should be trialled at a time, although later consideration may be given to trials of drug combinations.

The drugs used to treat neuropathic pain can be conveniently divided into two types: medications used to treat other conditions but found to be useful in reducing pain from nervous system damage, and analgesics.

### Antidepressants

Tricyclic antidepressants have long been used to treat all forms of neuropathic pain.<sup>3</sup> Clinical experience would suggest that antidepressants are often very helpful, especially in cases of peripheral neuropathic pain, as long as the starting dose is low (for example amitriptyline 10–12.5 mg at bedtime) and is increased slowly at intervals of a few days to a week. The maximum effective dose is disputed, but usually 75 mg at night is sufficient. The mean numbers needed to treat to obtain

a beneficial outcome, set at 50% reduction of pain, calculated in the early studies of amitriptyline were impressive at 2–3, but failed to take account of high dropout rates. Doses higher than 75 mg are associated with anticholinergic adverse effects on brain, bladder, bowel and blood pressure. Dry mouth is inevitable but weight gain is uncommon. If a benefit is to be obtained, it occurs within a few days of starting treatment. This benefit appears to be independent of the antidepressant effect.

Evidence for the use of other antidepressants apart from tricyclics is very limited. Venlafaxine may be useful.<sup>4</sup> Again, the dosing advice is to 'start low and go slow'. The effective dose may be as much as 225 mg daily.

### **Anticonvulsants**

There is a long tradition of using antiepileptic drugs in neuropathic pain, but they can all cause adverse effects such as drowsiness, dizziness and ataxia. Until recently there was almost no evidence of efficacy, but newer drugs such as gabapentin and pregabalin have been more extensively studied in patients with diabetic neuropathy and post-herpetic neuralgia. These two drugs modify the action of voltage-gated calcium channels of primary afferents so appear to interfere with the release of substance P, noradrenaline and the excitatory amino acid neurotransmitter glutamate.

The number of patients who need to be treated with gabapentin for one to have a 50% reduction in pain has been calculated as five.<sup>3,5,6</sup> Gabapentin should be started at 100 mg daily in older frail people and those with renal impairment, and the dose increased every few days to achieve symptomatic relief of pain. The effective dose ranges widely.

Pregabalin has a similar action to gabapentin, but caution is needed as experience of the drug is limited. Efficacy data are available in post-herpetic neuralgia<sup>7</sup> and painful diabetic neuropathy.<sup>8</sup> The number needed to treat is 4.2.<sup>3</sup> Caution is needed with the old and frail, and a slow increment from 75 mg daily to 75 mg twice a day by the end of the first week is likely to be better tolerated. Patients rarely want to exceed 150 mg twice a day because of the adverse effects common to antiepileptic drugs, plus blurred vision and oedema. Gabapentin and pregabalin should only be used after checking renal function, preferably by calculated creatinine clearance, as they are renally excreted.

Lamotrigine is another antiepileptic drug which has been used in neuropathic pain, but of the six randomised controlled trials so far reported, none has exceeded 40 patients. Similarly, there are no large randomised controlled trials of valproate and trials of topiramate have had conflicting results. There are no substantive studies to support the use of carbamazepine in the treatment of neuropathic pain, in contrast to its use in the true neuralgias. Drug concentration monitoring is not used in the treatment of neuropathic pain with antiepileptic drugs. Tolerance of the adverse effects is the limiting factor.

### **Analgesics**

Simple analgesics are often ineffective in neuropathic pain, but frequently there is a nociceptor component to the patient's pain. All analgesics have adverse effects and are therefore introduced incrementally over weeks to achieve a balance between pain relief and tolerance of adverse effects.

### **Opioids**

Pain which has not been responsive to other drugs may respond to opioids. This benefit is not seen in pain syndromes of uncertain origin including complex regional pain syndrome type 1 (reflex sympathetic dystrophy), fibromyalgia, irritable bowel syndrome and tension headache.

Opioids are started at low doses, such as oxycodone 5 mg or morphine 10 mg twice daily. These are increased progressively over days to a level which provides symptomatic relief with tolerable adverse effects. Patients can then be switched to controlled release formulations twice daily. If patients do not respond to moderate doses, such as oxycodone 40 mg or morphine 60 mg twice daily, do not increase the dose further as they are unlikely to respond to higher doses which have an increased risk of adverse effects.<sup>9</sup> Although prophylactic use before a pain-inducing activity is sometimes warranted, slow-release formulations, taken at fixed time intervals regardless of the presence of pain, are to be preferred to using analgesia only when pain occurs. Other medications to treat the common adverse effects of opioids may be needed. Constipation will almost invariably need to be treated.

For tramadol the number needed to treat was 3.9 in one meta-analysis<sup>3</sup>, but the doses used were relatively high. This may increase the chance of adverse effects such as headache, seizures and, especially when used in combination with an antidepressant, the serotonin syndrome.<sup>10</sup>

### **Other medications**

There is a limited role for other drugs when antidepressants, anticonvulsants and opioids have not worked. This often occurs during exacerbations of pain. The drugs tried have included ketamine, an N-methyl-D-aspartate antagonist delivered by parenteral and nasal routes, usually in a specialist setting, clonidine by the intrathecal and epidural routes, and local anaesthetics by topical, oral, parenteral, epidural and intrathecal routes. There is no indication for the use of non-steroidal anti-inflammatory drugs in patients with neuropathic pain unless there is clear clinical evidence that a nociceptor pain source is contributing to the patient's pain.

### **Neuralgias**

The treatment of neuralgias, apart from post-herpetic 'neuralgia', can be considered separately as they have a somewhat different pathophysiology and are not associated with sensory abnormalities on examination. They are triggered by non-noxious stimuli, leading to ectopic spread of afferent

impulses from large to small neurons, predominantly in dorsal root ganglia rather than sensitisation in central pathways as occurs in neuropathic pain. This manifests clinically as explosive high frequency bursts of paroxysmal pain.

These syndromes are generally responsive to carbamazepine, presumably acting as a sodium channel blocker. It is used in doses sufficient to alleviate paroxysms without producing unacceptable adverse effects. The starting dose varies, but, because these patients are often old and frail, should usually be 50 mg or 100 mg. Carbamazepine may even be effective at this dose, but usually needs to be increased over a few days according to the patient's tolerance of adverse effects such as drowsiness and dizziness. When to decrease the dose once an attack is controlled is always problematic. An attempt should be made to do so 1–2 weeks after control has been achieved. Despite gradual reduction it is often difficult to cease the dose and so a maintenance dose may be needed.

If carbamazepine is unhelpful, there are a number of second-line drugs, none of which has been adequately studied. They include oxcarbazepine, lamotrigine, gabapentin and baclofen. Early referral for surgery should be considered if control is difficult to obtain in patients with trigeminal neuralgia.

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## Further reading

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[R] randomised controlled trial

[S] company sponsored trial or publication

*Dr Helme is a member of the neuropathic pain advisory board for pregabalin, manufactured by Pfizer.*

See also **Dental notes**, page 82

## Self-test questions

*The following statements are either true or false (answers on page 87)*

5. A sensory deficit is often present in areas of the body affected by neuropathic pain.
6. Selective serotonin reuptake inhibitors can effectively reduce neuropathic pain in most patients.

## Patient support organisation

### Trigeminal Neuralgia Association of Australia

The Trigeminal Neuralgia Association provides information and support to patients, families and friends of those with trigeminal neuralgia. In addition there are support groups in most states (New South Wales, Victoria, Queensland and South Australia). Members receive monthly newsletters. The Association is affiliated with the US Trigeminal Neuralgia Association.

Phone: (02) 4579 6226

Email: [tna\\_sydney@yahoo.com](mailto:tna_sydney@yahoo.com)

Website: [www.tnaaustralia.org.au](http://www.tnaaustralia.org.au)

US website: [www.tna-support.org](http://www.tna-support.org)