

# The use of anticonvulsants for neuropathic pain

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## SYNOPSIS

Neuropathic pain is a common, although under-identified, condition which is frequently mistreated. With the exception of carbamazepine for trigeminal neuralgia, there is little evidence to support the use of anticonvulsants as first-line treatment. There is evidence from randomised controlled trials that gabapentin has an effect in diabetic neuropathic pain and post-herpetic neuralgia. These indications are not approved in Australia and the high cost of gabapentin precludes its indiscriminate use. To identify effective drugs an anticonvulsant can be tried, but prolonged use should be avoided if there is no clinical benefit.

**Index words:** analgesia, carbamazepine, gabapentin.

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## Neuropathic pain

Neuropathic pain affects approximately 1% of the population. Lesions or dysfunction of the peripheral and central nervous system can result in pain (see box). Complex regional pain syndrome I (previously termed reflex sympathetic dystrophy) and complex regional pain syndrome II (previously termed causalgia) are generally assumed to have a neuropathic basis. In addition, there is growing evidence that a range of other diffuse pain syndromes, such as fibromyalgia, may be caused by a central neuropathic dysfunction.

Neuropathic pain may be recognised by its association with disease, e.g. diabetes mellitus or multiple sclerosis, and by its characteristics, classically burning or electric, and often shooting or stabbing. A neuropathic cause may be inferred from a physical examination in which:

- pain is felt to non-noxious stimuli such as light pressure (mechanical allodynia)
- widespread painful sensation of abnormal severity following noxious stimulation (hyperalgesia) crosses musculoskeletal boundaries
- there is an exaggerated response to a painful stimulus in an area where there is an increased threshold for sensory detection (hyperpathia).

This is especially so when the pain is present in an area of sensory loss and in the absence of signs or investigations indicating a systemic inflammatory cause. Failure to recognise

the underlying neurological aetiology can lead to futile attempts to treat presumed local musculoskeletal causes.

## Efficacy of anticonvulsants

How anticonvulsants might improve pain states is much discussed and often oversimplified. Most anticonvulsants may affect pain indirectly through their effect on mood and sleep. Level 1 evidence from three randomised controlled trials shows that about 70% of patients with trigeminal neuralgia treated with carbamazepine will have a significant response.<sup>1-3</sup> The evidence in other neuropathic conditions is much weaker. A single crossover study of carbamazepine on pain related to diabetic neuropathy showed that 30% more patients had clinically significant pain relief with two weeks of treatment compared with placebo.<sup>4</sup> However, carbamazepine was found to be inferior to amitriptyline and not significantly better than placebo in a 1989 study of central post-stroke pain.<sup>5</sup>

The results of trials of phenytoin for the pain of diabetic neuropathy have been mixed.<sup>6,7</sup> Sodium valproate was not significantly better than placebo in patients with neuropathic pain due to spinal cord injury.<sup>8</sup> There is no high level evidence to support an effect for clonazepam on neuropathic pain.

Despite a lack of evidence from clinical trials to support their role, gabapentin and lamotrigine have been increasingly used by pain clinics. However, two recent large trials have shown the potential clinical usefulness of gabapentin in diabetic neuropathy and post-herpetic neuralgia.<sup>9,10</sup> Gabapentin is the first anticonvulsant to be shown to have an effect on post-herpetic neuralgia.

## Adverse effects of anticonvulsants

All of the older anticonvulsants have the potential for serious adverse reactions. Carbamazepine, phenytoin and sodium

### Conditions causing neuropathic pain

- trigeminal neuralgia
- post-herpetic neuralgia
- peripheral and entrapment neuropathy
- arachnoiditis
- brachial plexus avulsion pain
- phantom limb pain
- spinal cord injury pain
- post-stroke pain

valproate may cause hepatic dysfunction and blood dyscrasias. The need for blood testing is a disadvantage in a group of patients in which reduction of fear and anxiety is an important goal. Clonazepam has the potential to create physical dependency. Added to this are the more common adverse effects of impaired mental and motor function.

Gabapentin has a low incidence of serious adverse drug reactions, however, drowsiness, confusion and ataxia are common. The drug may have to be stopped even if it has improved the pain. Unlike most anticonvulsants, gabapentin may be used in patients with hepatic impairment, although the dose needs adjustment in renal impairment. The approved indications for gabapentin restrict its use to epilepsy. If it was used for pain at the dose used in the two published randomised controlled trials (3600 mg/day), it would cost at least \$4000 to treat one patient for a year. It is far from clear that such a high dose is necessary and in local, open label use, as little as 600 mg/day has been found to be effective. Nevertheless, its current cost precludes its indiscriminate use.

### Anticonvulsant use as part of a broader pain management approach

There are no 'magic bullets' for neuropathic pain. Pharmacological treatment used in isolation is almost certainly destined to induce frustration on the part of the patient and their physician. Active management of the physical, psychological and social results of chronic neuropathic pain is essential to good outcomes and frequently requires the assistance of a multidisciplinary pain service.

### Rational prescribing of anticonvulsants for neuropathic pain

Excessive use of multiple drugs is a common problem in patients with chronic neuropathic pain. At times, it may be the major management problem. Physicians treating patients with chronic neuropathic pain should be aware of the factors that can lead to ineffective medications being continued long term. Pain is a placebo responsive condition: a response to drugs of marginal effectiveness, such as anticonvulsants, may well be misinterpreted by a hopeful patient and physician as an active pharmacological effect. Patients commonly attempt to please their doctors when reporting their response to a new medication. Regression to the mean effect refers to the tendency of the patient and physician to start medications when symptoms are at, or nearing, their worst and mistaking the natural regression of the pain to its baseline as a 'drug effect'. In the longer term, patients often continue otherwise ineffective medications because of a fear that their pain will be even worse if they stop. In the case of clonazepam, withdrawal symptoms on reducing or stopping treatment can be misinterpreted as evidence of its positive effect on the painful condition.

These powerful forces to long-term overprescription may be minimised by setting goals of therapy before a time-limited trial of the anticonvulsant. The goals of treatment should include improvements in pain-related disability as well as pain

itself. They are usually best recorded in a diary form and rated numerically where possible. An 'untrial', or withdrawal of treatment, using the same review of outcome measures, is frequently appropriate before continuing the drug for the long term. Although challenging to organise logistically, N of 1 trials<sup>11</sup> can be justified before the long-term use of expensive or potentially dangerous medications that have little or no evidence to support their use in neuropathic pain.

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### Self-test questions

*The following statements are either true or false (answers on page 151)*

5. Gabapentin may help to reduce the pain of post-herpetic neuralgia.
6. An anticonvulsant may indirectly improve chronic pain by affecting mood.

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