

## Navigating the maze of drug therapy for neuropathic pain

Managing neuropathic pain is challenging whatever the cause.<sup>1,2</sup> Only half of those treated with drug therapy gain partial pain relief.<sup>3</sup> Prescribers are faced with an array of drugs with varying efficacy and often troublesome adverse effects.

Other considerations, such as co-morbidities, concomitant medicines and cost add to the complexity of selecting the best drug therapy for a particular patient. Drug therapy is best used as part of a multifaceted, active self-management approach to the physical, psychological, social and vocational impacts of chronic neuropathic pain (and may require the assistance of a multidisciplinary pain service).<sup>4,5</sup> This NPS News focuses on the different approaches to drug therapy for the neuropathic pain conditions most often seen in primary care: diabetic neuropathy, postherpetic neuralgia and trigeminal neuralgia (Box 1).

### Box 1: Common neuropathic pain conditions managed in primary care<sup>1,6-8</sup>

Type of neuropathic pain	What are the symptoms?	How common is it?
<b>Diabetic neuropathy</b> several different presentations, the most common is chronic diabetic peripheral neuropathy	Pain in the feet and ankles, known as the 'glove and stocking' distribution	Prevalence estimated as 15% of people with diabetes
<b>Postherpetic neuralgia</b>	Burning, aching, boring sensations or paroxysmal shock-like stabbing	Prevalence estimated as 7% to 27% of people with herpes zoster and increases with age
<b>Trigeminal neuralgia</b> usually occurs in the distribution of one or more branches of the trigeminal nerve	Sudden, brief, very severe paroxysms of pain, usually on one side of the face	Incidence estimated as 5–8 per 100 000 people per year and increases with age Twice as common in females as in males

## Treat early to prevent transition to persistent pain

Neuropathic pain needs to be managed aggressively to reduce the risk of transition to persistent pain.<sup>1,2</sup> Once established, it is difficult to treat particularly when neuronal damage is irreversible.<sup>2,9</sup>

Guidelines recommend starting drug therapy with a tricyclic antidepressant or an anti-epileptic (see insert, Table 1). Unless there is nociceptor stimulation, most neuropathic pain is refractory to simple analgesics (although a short trial of paracetamol, aspirin or a nonsteroidal anti-inflammatory drug can be tried)<sup>1</sup> with a limited role for opioids, including tramadol (see page 3).

Consider non-drug strategies: they help to reduce and manage neuropathic pain (see page 4).

Start with one drug at a time. Allow a trial period to assess response (see *Assessing effectiveness of drug therapy* page 2). Combination therapy with drugs from more than one class may be needed as several mechanisms can contribute to neuropathic pain (e.g. generation of ectopic impulses from damaged nerves, wind up and long-term potentiation of central nerve pathways).<sup>1,10,11</sup>

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## Assessing effectiveness of drug therapy

Discuss and agree on realistic treatment goals with patients and their carers.<sup>3</sup> Treatment goals should include improvements in pain-related disability as well as pain itself, and minimising adverse effects from drug therapy.<sup>4,9</sup> It is unlikely that pain will be eliminated completely but symptoms can be reduced to a tolerable level. Ask patients to regularly record pain intensity, functioning levels and any adverse effects from drug therapy.<sup>12</sup> Confirm that drug therapy is still effective by a trial discontinuation using the same recording of outcome measures — this may be appropriate before continuing therapy for the long term.<sup>4</sup>

Unidimensional tools (e.g. visual analogue scale) are inadequate for assessing neuropathic pain because they only assess pain intensity.<sup>12</sup> Multidimensional tools (e.g. Brief Pain Inventory\*) provide more information about pain history, intensity and associated disability.<sup>12</sup> Specific tools have been developed for neuropathic pain but have only been validated in small numbers of people (n = 40–180) across a wide range of neuropathic pain conditions.<sup>13–15</sup>

### Choosing drug therapy: limitations of the evidence

There is limited evidence for the efficacy of drugs used in neuropathic pain (hence there is no generally accepted 'step-wise' approach). Most drugs have been assessed in small short-term trials that used a variety of different patient populations and outcome measures (most considered a 50% reduction in pain a suitable threshold for efficacy).<sup>1,16</sup> Few trials directly compared different drugs (alone or in combination) and many had inadequate controls (making it difficult to assess the 'placebo' response). The number needed to treat† (NNT) and the number needed to harm‡ (NNH) — from well-conducted meta-analyses — can help prescribers choose the most effective drug with the most tolerable adverse effect profile.<sup>17–19</sup>

### Antidepressants and anti-epileptics: which drugs and when?

Start with a tricyclic antidepressant or an anti-epileptic (see insert, Table 1). These drug classes have been shown to be effective for neuropathic pain. However, some drugs are not approved by the Therapeutics Goods Administration or subsidised by the Pharmaceutical Benefits Scheme for neuropathic pain (see insert, Table 2).

**Tricyclic antidepressants** appear to relieve pain independently of their antidepressant effect and at smaller doses than required for depression.<sup>1</sup> Amitriptyline and nortriptyline are the most studied and are similarly effective for diabetic neuropathy (NNT = 1.3) and postherpetic neuralgia (NNT = 2.7).<sup>3,17</sup> Other tricyclic antidepressants offer no advantage and have been less well studied. There is some evidence for serotonin–noradrenaline reuptake inhibitors (venlafaxine, duloxetine) and limited evidence for selective serotonin reuptake inhibitors for diabetic neuropathy.<sup>7,16,17</sup>

Consider either amitriptyline or nortriptyline for initial treatment of diabetic neuropathy and postherpetic neuralgia.<sup>1,7,20</sup> Trial for 6–8 weeks before assessing response (with at least 2 weeks at the maximum tolerated dose).<sup>3</sup> The NNH for minor adverse events (e.g. constipation, drowsiness) is 6.<sup>17</sup>

People who do not respond to amitriptyline may respond to nortriptyline.<sup>21</sup> Nortriptyline is less likely than amitriptyline to cause hypotension, drowsiness and anticholinergic adverse effects, so may be useful in the elderly.<sup>9</sup>

\* Available at [www.hnehealth.nsw.gov.au/pain/health\\_professionals/assessment\\_tools](http://www.hnehealth.nsw.gov.au/pain/health_professionals/assessment_tools).

† NNT = the number of people that need to be treated with a given drug for one person to experience at least 50% pain relief.

‡ NNH = the number of people that need to be treated with a given drug for one person to experience a minor adverse effect.

The gamma-aminobutyric acid (GABA) analogues — gabapentin and pregabalin — appear to relieve pain by interfering with the release of substance P, noradrenaline and glutamate.<sup>1</sup> They may be a useful adjunct for people already taking other anti-epileptic drugs as there are no known drug–drug interactions.<sup>9</sup>

**Gabapentin** is effective for diabetic neuropathy (NNT = 2.9) and postherpetic neuralgia (NNT = 3.9).<sup>18</sup> It is an alternative to amitriptyline or nortriptyline for initial treatment.<sup>1,7,20</sup> Trial for 2 months before assessing response.<sup>3</sup> There is anecdotal evidence for its use in trigeminal neuralgia when carbamazepine is contraindicated or not tolerated.<sup>22</sup> The NNH for minor adverse events (e.g. dizziness, drowsiness) is 3.7.<sup>18</sup>

**Pregabalin** is a structural analogue of gabapentin. It may be as effective as gabapentin for diabetic neuropathy and postherpetic neuralgia, but it has less efficacy and safety data.<sup>16,23</sup> Consider pregabalin when amitriptyline, nortriptyline or gabapentin inadequately control pain. Trial for 4 weeks before assessing response.<sup>3</sup>

**Carbamazepine** is first choice for trigeminal neuralgia, with an NNT = 1.9 for any trigeminal neuralgia pain relief and NNT = 2.6 for chronic trigeminal neuralgia pain.<sup>1,7,19,24</sup> Attacks of trigeminal neuralgia are brief and frequent so preventative drug therapy is needed. There is limited evidence for using carbamazepine in diabetic neuropathy<sup>1,19</sup> and it has little effect in postherpetic neuralgia.

Carbamazepine is initially effective for most people with trigeminal neuralgia but efficacy declines over a few years.<sup>22,25</sup> This requires either increasing the dose or adding/switching to a second drug.<sup>8</sup> It is unclear whether this decline in efficacy is due to tolerance to carbamazepine or disease progression.<sup>22</sup> Carbamazepine has complex pharmacokinetics (induces liver enzymes, interacts with other drugs) and sometimes severe adverse effects (NNH = 3.7), particularly in the elderly.<sup>9,16,19</sup>

## A limited role for opioids (including tramadol)

Refer people who may require opioids (including tramadol) — because they have not responded to or cannot tolerate other drugs — to a pain specialist and/or a neurologist wherever possible. These drugs have little benefit in trigeminal neuralgia but may be effective in the short term (1–10 weeks) for diabetic neuropathy and postherpetic neuralgia.<sup>8,22,26,27</sup>

There are no long-term data assessing efficacy, safety (e.g. in chronic use) or effects on quality of life for **opioids** in treating neuropathic pain.<sup>26</sup> More than 80% of people who start opioids stop taking them after a year because of their unfavourable benefit–harm profile.<sup>16</sup>

**Tramadol** is thought to exert its analgesic effects both through binding to mu opioid receptors and inhibiting both noradrenaline and serotonin reuptake. Its adverse effect profile (e.g. CNS effects) and drug interactions limit its usefulness. Avoid tramadol in people who are taking drugs that increase the risk of serotonin toxicity (e.g. selective serotonin reuptake inhibitors) or reduce the seizure threshold (e.g. tricyclic antidepressants).<sup>9</sup> The dose of tramadol needs to be reduced for people who have severe hepatic impairment or creatinine clearance < 30 mL/minute.<sup>9</sup>

## Topical preparations may be useful for some people

Topical capsaicin (0.075%) may be useful for diabetic neuropathy or postherpetic neuralgia if a tricyclic antidepressant or GABA analogue is contraindicated or not tolerated.<sup>7,20</sup> There is some evidence that capsaicin maintains its efficacy for at least 2 years.<sup>28</sup> On first application, capsaicin causes burning pain and increased sensitivity to painful stimuli. With repeated use it relieves pain by depleting substance P and other neuropeptides from Type C nerve fibres.<sup>10,29</sup>

There is limited evidence that topical lignocaine may provide short-term pain relief for people with postherpetic neuralgia.<sup>30,31</sup>

### Erratum: NPS News 58

In *NPS News 58*, NPS stated that "Single-ingredient inhalers containing a corticosteroid are neither TGA registered nor PBS listed for COPD." The second part of this statement is incorrect.

Inhaled corticosteroids are not TGA approved for COPD. However, they are listed on the PBS general schedule as unrestricted benefits and prescribers may write prescriptions in line with their clinical judgment.

### Erratum: NPS News 59

There was an error in Table 1 of *NPS News 59: Drugs used in dementia in the elderly*. The entry for the Severe Impairment Battery should have stated that lower scores on this scale indicate poorer function (not higher scores).

We apologise for any confusion.

## Non-drug strategies help to reduce and manage neuropathic pain

Consider non-drug strategies as part of any management plan.<sup>5</sup> Non-drug strategies (e.g. stress reduction, sleep hygiene and physiotherapy) help to reduce and manage neuropathic pain.<sup>1-3</sup> Psychological support (e.g. cognitive-behavioural therapy), transcutaneous electrical nerve stimulation (TENS), physical measures (e.g. cold water immersions) or alpha-lipoic acid may be tried for diabetic neuropathy.<sup>1,11</sup> For postherpetic neuralgia, ice massage or TENS may be tried.<sup>1</sup>

### Resources and information for patients

Provide patients with consumer medicines information (CMI) leaflets: information about adverse effects of medicines is important even though their neuropathic pain condition may not be mentioned in the CMI. Where relevant, explain to patients that although there may be some evidence for efficacy, their medicines may not be approved by the Therapeutics Goods

Administration or subsidised by the Pharmaceutical Benefits Scheme for their condition (see insert, Table 2).

People taking multiple medicines may benefit from strategies to help them adhere to drug therapy (e.g. a medicines list, available at [nps.org.au/medicines\\_list](http://nps.org.au/medicines_list)) and/or a Home Medicines Review.\*

Other resources include:

- Diabetes Australia ([www.diabetesaustralia.com.au](http://www.diabetesaustralia.com.au)) and the US National Institute of Diabetes and Digestive and Kidney Diseases ([www.diabetes.niddk.nih.gov/dm/pubs/neuropathies/](http://www.diabetes.niddk.nih.gov/dm/pubs/neuropathies/)) provide information for people who have diabetic neuropathy.
- The Trigeminal Neuralgia Association of Australia ([www.tnaaustralia.org.au](http://www.tnaaustralia.org.au)) provides information and support for people who have trigeminal neuralgia.
- The Neuropathy Trust ([www.neurocentre.com](http://www.neurocentre.com)) provides information for people who have neuropathic pain.

\* Medicare provides a rebate for a GPs' involvement in an HMR, MBS item 900.

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*The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.*



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