Pregabalin (Lyrica) for neuropathic pain
(pre-GAB-a-lin)

KEY POINTS

Pregabalin appears to have similar efficacy to that of amitriptyline and gabapentin for neuropathic pain
Pregabalin is superior in efficacy to placebo and appears to be non-inferior in efficacy and safety to amitriptyline and gabapentin (from indirect comparisons).

Consider initial treatment with another agent, such as a tricyclic antidepressant, before pregabalin
Pregabalin is only PBS listed for people with refractory neuropathic pain not controlled by other drugs (Authority Required).

Dizziness and drowsiness are common dose-dependent adverse events
In trials these were the most common adverse effects causing people to stop pregabalin.

Dosage reduction is required in people with impaired renal function

PBS listing

Authority required (Streamlined)
Refractory neuropathic pain not controlled by other drugs.

May be prescribed by nurse practitioners
Authorised nurse practitioners may prescribe this medicine. See the Pharmaceutical Benefits Scheme (PBS) website for more information on nurse practitioner PBS prescribing.

What is it?

Pregabalin is a structural analogue of the neurotransmitter GABA. It has analgesic, anticonvulsant, anxiolytic and sleep-modulating activities and is indicated for treatment of epilepsy and neuropathic pain. However, it should be noted that gabapentin is not PBS reimbursed for neuropathic pain.

Who is it for?

Pregabalin is a treatment option for people with refractory neuropathic pain who have not responded to other drugs. Use with caution in people with renal impairment, as pregabalin is renally excreted.

Where does it fit?

There is no generally accepted ‘stepwise’ approach to treating neuropathic pain. There is an array of drugs with limited evidence for differences in efficacy, and often with troublesome adverse effects. Drug therapy is best used as part of a multifaceted, multidisciplinary, active self-management approach to the physical, psychological, social and vocational impacts of neuropathic pain. Assess the nature of the pain experience and inform people of realistic outcomes with treatment. The primary goal in most cases is to make the pain tolerable — not usually to eliminate the pain. Aim for medium-term drug therapy with a drug holiday after 6 months. Patients who relapse during a drug holiday can resume treatment.
Guidelines recommend starting drug therapy for neuropathic pain with a TCA (amitriptyline or nortriptyline) or an antiepileptic agent (gabapentin or pregabalin).6–12 The dose of the drugs can be escalated at weekly intervals if tolerated, but it may take several weeks to achieve clinical efficacy.

**Consider initial therapy with amitriptyline or nortriptyline**

TCAs are an established first-line treatment option for neuropathic pain but are not approved by the Therapeutic Goods Administration (TGA) for this indication.6-12 Amitriptyline is the most studied TCA for neuropathic pain.13 TCAs exhibit significant adverse effects that limit their clinical use, particularly in elderly people.13 Anticholinergic adverse events, such as dry mouth, constipation and urinary retention, are common.13 In addition they may cause serious cardiovascular adverse effects, including postural hypotension, heart block and arrhythmias.13

**Gabapentin is effective for treating neuropathic pain**

Guidelines recommend gabapentin for the treatment of neuropathic pain.6-12 However, it is not reimbursed by the PBS for this indication. In a meta-analysis gabapentin was demonstrated to be effective for the treatment of a variety of neuropathic pain conditions.14 The number needed to treat (NNT) to benefit, as measured by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definition, were 6.8 (95% confidence interval [CI] 5.6 to 8.7) for substantial pain relief (50% over baseline) and 5.8 (95% CI 4.8 to 7.2) for moderate pain relief (35% over baseline).14

**Consider pregabalin for neuropathic pain refractory to other drugs**

In clinical trials pregabalin provided significant pain relief (see Table 1) and improved quality of sleep in both postherpetic neuralgia and painful diabetic neuropathy.15 Pregabalin has dose-dependent clinical efficacy and appears not to be effective at 150 mg/day for diabetic neuropathy.6

Preliminary evidence suggests that pregabalin may be effective in the treatment of trigeminal neuralgia.16–18 However, further clinical trial data are required before it can be recommended for this indication. The anticonvulsant carbamazepine remains the drug of choice for trigeminal neuralgia.6,8

**Consider combination therapy**

A significant proportion of people with neuropathic pain will not benefit from treatment with a single medication, even when administered at its maximum tolerated dose.2,19 Evidence suggests that at least 45% of people with neuropathic pain concurrently receive two or more drugs to treat neuropathic pain.20

<table>
<thead>
<tr>
<th>Pregabalin daily dose</th>
<th>Number of studies</th>
<th>Participants</th>
<th>Relative benefit* (95% CI)</th>
<th>At least 50% pain relief NNT (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postherpetic neuralgia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg</td>
<td>3</td>
<td>527</td>
<td>2.3 (1.6 to 3.4)</td>
<td>6.9 (4.8 to 13)</td>
</tr>
<tr>
<td>300 mg</td>
<td>4</td>
<td>713</td>
<td>2.5 (1.9 to 3.4)</td>
<td>5.1 (3.9 to 7.4)</td>
</tr>
<tr>
<td>600 mg</td>
<td>4</td>
<td>732</td>
<td>2.7 (2.1 to 3.5)</td>
<td>3.9 (3.1 to 5.1)</td>
</tr>
<tr>
<td><strong>Diabetic neuralgia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg</td>
<td>2</td>
<td>359</td>
<td>1.1 (0.8 to 1.6)</td>
<td>NA‡</td>
</tr>
<tr>
<td>300 mg</td>
<td>4</td>
<td>823</td>
<td>1.5 (1.2 to 1.8)</td>
<td>7.5 (5.1 to 14)</td>
</tr>
<tr>
<td>600 mg</td>
<td>6</td>
<td>1360</td>
<td>1.7 (1.5 to 2.0)</td>
<td>5.0 (4.0 to 6.6)</td>
</tr>
</tbody>
</table>

* Relative to placebo
† NNT were calculated from the combined results of clinical trials with different durations (4-14 weeks)
‡ Not effective at 150 mg
Combining two or more different drugs may improve analgesic efficacy and reduce overall adverse events if synergistic interactions allow dose reductions of combined drugs. However, combinations of medicines can be associated with increased adverse events.

A specific combination of treatments cannot be recommended due to the limited number of studies for any combination therapy, as well as other study factors, such as the limited trial size and duration. Clinical studies of pregabalin in combination with an antidepressant, a cyclo-oxygenase-2 (COX-2) inhibitor or an opioid have shown positive responses greater than the respective monotherapies in diabetic neuropathy and postherpetic neuralgia (five positive trials and one negative trial).

**Refractory severe neuropathic pain**

Assistance from a multidisciplinary pain service may be required for refractory, severe neuropathic pain, as treatment options are complex. The TGA has not approved some of the drugs recommended in guidelines for a neuropathic pain indication and most are not subsidised by the PBS for neuropathic pain.

Tramadol can be considered as a third-line treatment for refractory neuropathic pain. However, other opioids are not recommended without further pain-medicine specialist input due to the problems with tolerance and dependence. There is limited evidence for use of selective serotonin reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors in the treatment of neuropathic pain, and further research is required to establish their role.

**How does it compare?**

**Pregabalin is superior to placebo for the treatment of neuropathic pain**

A meta-analysis of randomised placebo-controlled trials demonstrated that pregabalin (300 mg, 450 mg and 600 mg daily) significantly reduced subjective pain compared with placebo for neuropathic conditions. Pregabalin administered as 150 mg/day was generally ineffective for diabetic neuropathic pain, and more had moderate benefit (at least 35% pain relief). After pregabalin treatment a minority of patients had substantial benefit (at least 50% pain relief), and more had moderate benefit (at least 35% pain relief). After treatment with pregabalin (300–600 mg daily) the Patient Global Impressions of Change (PGIC) rating of much or very much improved was achieved in about 35% of patients with postherpetic neuralgia and 50% of those with painful diabetic neuropathy. At all doses a significant proportion of patients had no, or trivial, benefit, or discontinued because of adverse events.
Limited evidence comparing pregabalin with amitriptyline and gabapentin

There are no adequately powered direct head-to-head trials comparing pregabalin with other drugs. There are indirect comparisons of pregabalin with amitriptyline and gabapentin using placebo as the common comparator.\(^\text{21}\) However, indirect comparisons have numerous limitations, as they compare different patient populations, primary outcomes and pain measurement scales.

The PBAC noted that indirect comparisons supported the conclusion that pregabalin was clinically no worse than amitriptyline and gabapentin.\(^\text{21}\)

The efficacy and safety of pregabalin and amitriptyline were demonstrated to be comparable in two head-to-head clinical trials in patients with diabetic peripheral neuropathy, but these were not powered to detect either superiority or non-inferiority of pregabalin versus amitriptyline.\(^\text{22,23}\)

A 36-day head-to-head dose titration trial in patients with diabetic peripheral neuropathy compared pregabalin (300 mg followed by 600 mg, \(n = 24\)), duloxetine (60 mg followed by 120 mg, \(n = 23\)) and amitriptyline (50 mg followed by 75 mg, \(n = 27\)).\(^\text{23}\)

All treatments improved subjective pain versus placebo as assessed by the primary outcome measure, the Brief Pain Inventory, and also the secondary outcome measure, the short-form McGill visual analogue scale, with no difference between treatments after 1 week of treatment.\(^\text{23}\)

Pregabalin appears to have some distinct pharmacokinetic advantages over gabapentin, with higher bioavailability, more rapid absorption and increased binding affinity.\(^\text{4}\) However, head-to-head trials are needed to provide evidence supporting the use of pregabalin over gabapentin in the treatment of neuropathic pain.

Safety issues

Pregabalin is generally well tolerated and is associated with dose-dependent adverse events that are mild to moderate and usually transient.\(^\text{5}\)

As pregabalin alters neurotransmission, it can cause a variety of neurological adverse events.

Common adverse effects reported in at least 3% of all patients treated with pregabalin include:\(^\text{12}\)

- dizziness
- drowsiness
- blurred vision
- fatigue
- weight gain
- dry mouth
- headache
- impaired balance
- peripheral oedema.

Report suspected adverse reactions to the TGA online (www.ebs.tga.gov.au) or by using the ‘Blue Card’ distributed three times a year with Australian Prescriber. For information about reporting adverse reactions, see the (www.tga.gov.au).

Dizziness and drowsiness: the most common reason for stopping pregabalin therapy

In clinical trials dizziness and drowsiness were commonly reported (28–36% and 20–24% of patients, respectively, taking pregabalin 300 mg/day).\(^\text{1}\) Both adverse effects occurred more often at higher doses and were the most common reasons for stopping pregabalin.\(^\text{1}\)

About one-third of people reported dizziness and about half reported drowsiness persisting throughout therapy.\(^\text{1}\)

Weight gain

Weight gain occurred more frequently in patients treated with pregabalin compared with placebo.\(^\text{1}\) This dose-dependent side effect may be problematic for patients, such as those with diabetes, who may need to adjust hypoglycaemic medications.\(^\text{1}\)

Occurrence of peripheral oedema

In randomised controlled trials, peripheral oedema was seen more frequently in people with neuropathic pain treated with pregabalin than in those in the control group.\(^\text{1,24}\) This may be a particular concern with the higher incidence of peripheral oedema in people with diabetes.\(^\text{24}\)
Congestive heart failure
There have been postmarketing reports of congestive heart failure in some people receiving pregabalin.1

Depression and anxiety
Neuropathic pain can be severe and unrelenting; thus it is important to recognise and treat comorbidities such as anxiety and depression.4 In addition, anticonvulsant drugs, including pregabalin, increase the risk of suicidal thoughts or behaviours in people using them for any indication.25,26 Monitor people treated with pregabalin for the emergence or worsening of depression, suicidal thoughts or self-harm behaviour and/or any unusual changes in mood or behaviour.1

Reason for PBS listing
The PBAC recommended pregabalin for listing on the basis of an indirect comparison with amitriptyline and gabapentin with placebo as the common comparator. The PBAC accepted that pregabalin was clinically superior to placebo and clinically no worse than amitriptyline or gabapentin.21

The PBAC recommended listing of pregabalin on the basis of acceptable cost-effectiveness compared with placebo in people with uncontrolled neuropathic pain. It noted the clinical need for an alternative to current treatments for neuropathic pain.21

A key issue identified by the PBAC was economic uncertainty from the potential for pregabalin use outside the restriction. They considered that it was essential that the drug utilisation subcommittee (DUSC) review usage 12 months after PBS listing.21

Dosing issues
Start with 75 mg twice a day for 3–7 days. If required, increase dose to 150 mg twice a day after 3–7 days, to a maximum of 300 mg twice a day after another 7 days.1 It may take several weeks to achieve maximal effect with pregabalin. If improvement is satisfactory continue treatment and consider gradually reducing the dose over time if improvement is sustained.9

Discontinue pregabalin if it does not improve symptoms or is not tolerated by tapering the dose over a minimum of 1 week, or longer depending on the dose and duration of therapy.1 Abrupt withdrawal may result in adverse events, including insomnia, headache, nausea, anxiety, hyperhidrosis and diarrhoea.1

Adjust the dose in renal impairment: refer to the product information for details.1

Conduct early and regular clinical reviews
Due to the refractory nature of neuropathic pain, conduct early and regular clinical reviews to monitor the effectiveness of the chosen treatment.9 The review should assess:

- pain (utilise multidimensional tools, such as the Brief Pain Inventory, that provide information about pain history, intensity and associated disability)
- adverse events
- daily activities (e.g. ability to work or drive)
- mood (particularly if the person may be depressed and/or anxious)
- quality of sleep
- subjective, overall self-reported improvement in pain (e.g. using PGIC).9

Information for patients
Discuss the Lyrica consumer medicine information (CMI) leaflet with the patient and inform about common side effects such as dizziness and drowsiness. Monitor for weight gain and advise that constipation, diarrhoea, nausea, headache, weight gain, dry mouth or blurred vision may occur, and that, if they are affected, not to drive or operate machinery.

Advise patients not to stop taking pregabalin suddenly. Stopping suddenly may cause anxiety, insomnia, headache, sweating, nausea and diarrhoea.

Advise that it may take several weeks to achieve maximal effect for postherpetic neuralgia.

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**Additional Information**


REFERENCES


Updated April 2013 to reflect PBS listing effective from 1 March 2013.

First published: December 2012.

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