

Use of gabapentinoids for non-seizure indications

Summary of Formulary listings

- Pregabalin is listed “for use in refractory neuropathic pain” in line with the PBS criteria.
- Gabapentin is listed “for use in paediatric patients on the advice of a neurology or pain service”.

Recommendations for use of gabapentinoids in non-seizure indications

1. Do not use gabapentinoids for pain that is not of a neuropathic origin.
2. Trial the following first line neuropathic pain medicines (where appropriate) before gabapentinoid use:
 - amitriptyline
 - duloxetine
 - carbamazepine (first line for trigeminal neuralgia)
 - consider lidocaine (lignocaine) patches for post herpetic neuralgia or for localised neuropathic pain on the advice of pain, palliative care or spinal services.
3. Before starting a gabapentinoid for neuropathic pain, be aware that most patients will not achieve clinically useful pain relief¹.
 - Assess response (pain intensity, quality of life and patient function² after 4 weeks and gradually stop treatment if no improvement is seen.
 - Reassess ongoing need by gradually reducing treatment every 3–6 months.

Background

The exact mechanism of action of gabapentinoids is unclear. They are structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but do not significantly affect GABA or its receptors. The mechanism of action is more likely due to binding to the alpha-2 delta protein subunit of high threshold voltage-dependent calcium channels, reducing calcium influx and neurotransmitter release^{1,3,4}.

Pregabalin is Therapeutic Goods Administration (TGA) approved for the treatment of neuropathic pain (in adults) and as adjunctive therapy in adults with partial seizures³.

- Pregabalin is listed on the Pharmaceutical Benefits Scheme (PBS) for refractory neuropathic pain.

Gabapentin is TGA approved for treatment of neuropathic pain and partial seizures, as add-on therapy in adults and children over 3 years who have not achieved adequate control with standard antiepileptic medicines⁴.

- Gabapentin is listed on the PBS for partial epileptic seizures and on the Repatriation Schedule of Pharmaceutical Benefits (RPBS) for refractory neuropathic pain.

While registered for adjunct or add on therapy for partial seizures, the use of gabapentinoids has largely been superseded by newer, better tolerated therapies.

Efficacy

Neuropathic pain

There is a lack of quality comparative efficacy data for gabapentinoids in the management of neuropathic pain.

- A 2017 Cochrane review⁵ (37 studies of 5914 adult participants) concluded that gabapentin at doses of 1800 – 3600 mg per day can provide good levels of pain relief to some people with postherpetic neuralgia and peripheral diabetic neuropathy. Evidence for other types of neuropathic pain is very limited. Over half of those treated with gabapentin will not have worthwhile pain relief but may experience adverse events.
- A 2019 Cochrane review⁶ (45 studies of 11,906 adult participants) concluded that pregabalin shows efficacy in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain. There was no or inadequate evidence of efficacy in HIV neuropathy and central neuropathic pain. “It was found that some people will derive substantial benefit with pregabalin; more will have moderate benefit, but many will have no benefit or will discontinue treatment”.
- The Pharmaceutical Benefits Advisory Committee concluded in their pregabalin efficacy assessment that pregabalin was superior to placebo and non-inferior to amitriptyline and gabapentin⁷.

There is significant heterogeneity in neuropathic pain symptoms and the underlying mechanism of pain⁸. A systematic review identified most neuropathic pain studies⁹:

- were conducted in diabetic neuropathy or postherpetic neuralgia
- publication bias accounted for approximately 10% of the treatment effect
- placebo effect was large and drug effects were modest
- most studies were for 12 weeks or less
- no specific drug or drug class is superior in any neuropathic pain syndrome, except trigeminal neuralgia where carbamazepine/oxcarbazepine are first line¹⁰.

Off-label indications

Gabapentinoids have increasingly been used for off-label indications including mood disorders, treatment of drug and alcohol addiction, low back pain and restless legs syndrome. Reliable evidence is not available to support many of the off-label uses of gabapentinoids. Court documents released in the USA suggest that some of the off-label use of gabapentin was driven by deceptive and illegal marketing practices¹¹. There are also significant concerns about the integrity of data submitted for off-label gabapentin uses, which has resulted in fines for fraudulent scientific evidence².

Gabapentinoids have increasingly been prescribed off-label for use as an adjuvant to opioid therapy for pain that is not of a neuropathic origin (e.g., acute pain and chronic non-cancer pain)¹² however there is a lack of comparative efficacy evidence. The Australian and New Zealand College of Anaesthetists (ANZCA) 2022 position statement on acute pain states “*Once commonly recommended for inclusion in multimodal analgesia regimens, it is now recognised that the benefits of these medications have been over-estimated and potential harms under-estimated*¹³.”

Safety concerns

Adverse effects from gabapentinoids are frequent and include drowsiness, sedation, confusion, euphoria, ataxia and visual disturbances (e.g. blurred vision, diplopia)¹. The combination of gabapentinoids with opioids and other central nervous system (CNS) depressants have additive toxicity and can lead to serious side effects including sedation, respiratory depression, coma and death¹⁴. Gabapentinoids have been shown to pose a risk of misuse, abuse and dependence. They are used recreationally for euphoric effects which are dose dependent.

Although both gabapentinoids have significant toxicity concerns, it remains unclear if one is less toxic – as numbers of users and dose-effect data for morbidity and mortality are not routinely collected⁸. ‘Boxed Warnings’ were added to pregabalin and gabapentin in 2021 advising prescribers to assess a patient's risk of misuse (for pregabalin), and abuse or dependence (for pregabalin and gabapentin) and to monitor patients regularly during treatment¹⁴. Pregabalin is also monitored by SafeScript NSW¹⁵.

Gabapentinoid Formulary reviews

Adult indications:

Pregabalin is listed as the gabapentinoid on the Formulary for use in neuropathic pain, as per the PBS criteria. The NSW Medicines Formulary Committee (the Committee) considered the efficacy of gabapentinoids in neuropathic pain, safety concerns, abuse potential, continuity of supply via the PBS and the aims of rationalising listings within the same class.

Gabapentin has not been listed for use in adult populations. Initiation of gabapentin in the adult population requires local DTC approval via the Individual Patient Use (IPU) pathway. Patients should be monitored to assess the benefit and effect of gabapentinoids as per the recommendations on page one.

Paediatric indications:

Gabapentin is listed as the gabapentinoid on the Formulary for paediatric patients, on the advice of a neurology or pain service.

The Committee considered the following information when it reviewed the off-label use of gabapentin for pain management in paediatric settings:

- Not all first line medicines used for management of neuropathic pain in adults are directly applicable/appropriate in paediatric populations.
 - There is limited experience with use of pregabalin and duloxetine in paediatric populations, and some evidence suggesting risk of harm is greater in adolescents compared to adults with pregabalin.
- The presentation, diagnosis and treatment of differential pain conditions may be more complex in paediatric patients, particularly in those with significant disabilities and complex healthcare needs.

The Committee agreed on two recommendations as part of the decision to list gabapentin:

- i. Specialist paediatric networks/services to develop consensus treatment guidance for gabapentin use in paediatric patients.
- ii. Medicine use evaluations (MUE) evaluating treatment outcomes in off-label gabapentin in paediatric populations are required.

The NSW Medicines Formulary Committee Secretariat will continue to work with specialist paediatric networks/services on the above recommendations.

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