A GUIDE TO

deprescribing

phn TASMANIA
An Australian Government Initiative

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

GABAPENTINOIDS

KEY POINTS

Gabapentinoids are effective for some patients with neuropathic pain, but typically only 1 in 8 patients obtain a benefit.

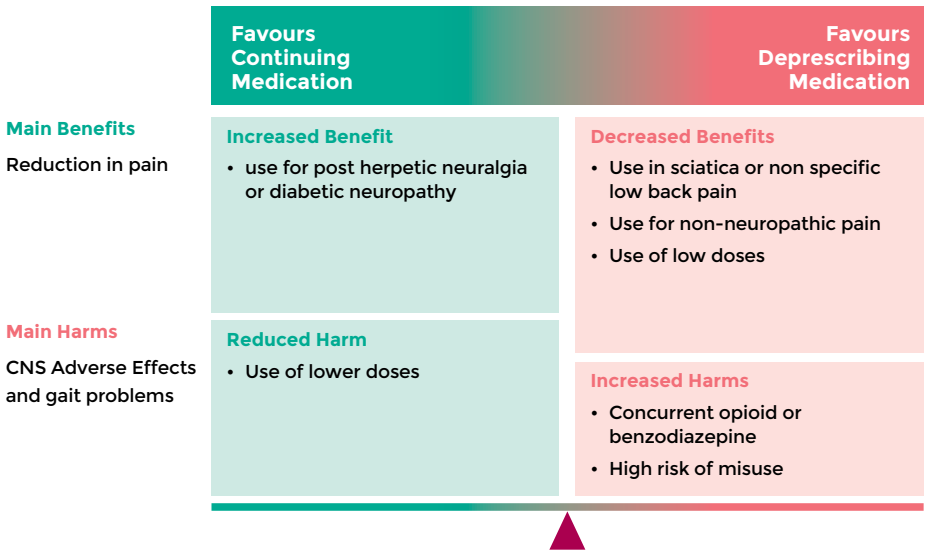
Amitriptyline, nortriptyline or duloxetine, or non-pharmacological strategies are often as, or more, effective than gabapentinoids.

The high renal clearance of gabapentinoids means that patients with renal impairment are at particularly high risk of accumulation and adverse effects.

Gabapentinoids are not shown to be more effective than placebo for sciatica or non-specific low back pain.

Avoid co-prescribing gabapentinoids with other CNS depressants (opioids, benzodiazepines, antidepressants).

BENEFIT VERSUS HARM



RECOMMENDED DEPRESCRIBING STRATEGY

- Regardless of indication, trial dose reduction or deprescribing every 3-6 months to assess ongoing benefits and to reduce the risk of adverse effects.
- In patients without clear signs of neuropathic pain, gabapentinoids should be tapered and ceased where possible.

BACKGROUND

Use of gabapentinoids (gabapentin and pregabalin) has increased markedly since subsidisation of pregabalin on the Pharmaceutical Benefits Scheme (PBS) was introduced in 2013. In the 2020-2021 financial year, pregabalin was the 13th most prescribed medication in Australia with a total volume of over 4 million prescriptions and a total government cost of around $73.[1] Whilst the volume of gabapentin use is lower, largely due to very limited PBS criteria, significant numbers of patients are prescribed this medication privately, or obtain it on subsidised prescriptions through public hospitals in Tasmania. Although the gabapentinoids were originally developed to treat epilepsy, they are now primarily used as non-opioid analgesics in the management of pain. For information on the deprescribing of gabapentinoids when used in the management of epilepsy, please refer to the Deprescribing Antiepileptics guide.

Although neuropathic pain is the only TGA approved pain indication for both pregabalin and gabapentin, and the PBS listing for pregabalin is specifically for neuropathic pain refractory to other drugs, there is substantial use of gabapentinoids for other pain conditions, as well as smaller quantities for restless legs syndrome and anxiety.

A review of prescribing patterns in Australian general practice showed that almost two thirds of patients prescribed pregabalin had no recorded diagnosis of neuropathic pain[2] and many patients taking pregabalin did not have back problems or sciatica recorded as diagnoses. These results indicate that pregabalin is often used for other types of pain (see **Figure 1**).

Similar patterns of prescribing (i.e. high rate of "off-label" use) and increasing use have been recorded in the United Kingdom.[3, 4, 5]

Concerns over the frequency of adverse effects in vulnerable individuals and the potential for gabapentinoid misuse has prompted an Australian Department of Health Safety Advisory,[6] as well as a National Prescribing Service Practice Review to optimise safety in prescribing for neuropathic pain.[7] Reflecting these concerns, both the United Kingdom (in 2019) and the United States of America (in 2005) have scheduled gabapentin and pregabalin as controlled substances.[8,9]

In this guide, we review the efficacy and adverse effects of the gabapentinoids in a number of (non-epilepsy) indications and identify situations where reduction or cessation of the agent may be appropriate.

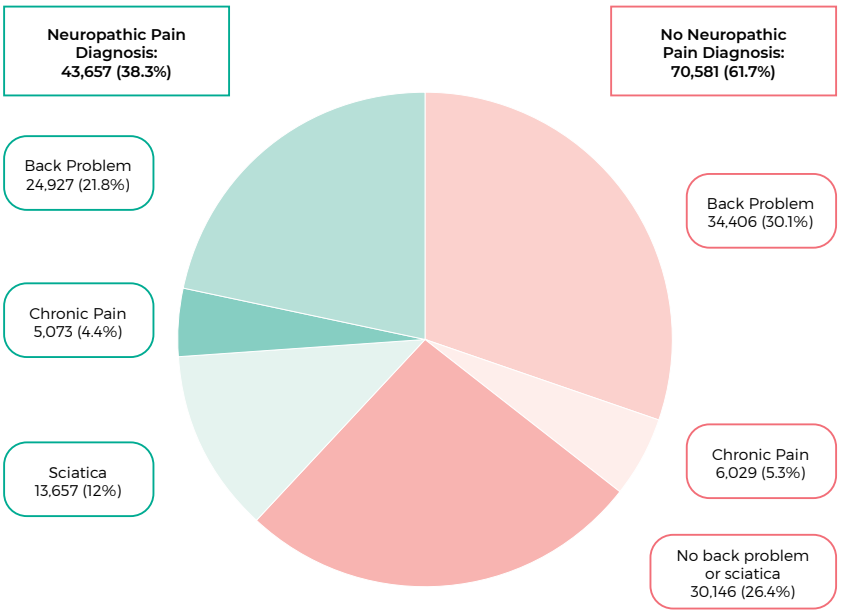


Figure 1: Pain diagnoses and conditions recorded in people prescribed pregabalin (Adapted from Ref 2)

EFFICACY

Although gabapentinoids are structurally similar to gamma-aminobutyric acid (GABA) they do not bind directly to GABA-A or GABA-B receptors. They do, however, bind to presynaptic calcium channels and increase production of an enzyme responsible for GABA production. The resultant CNS effect is a reduction in excitatory neurotransmitters and an increase in GABA, explaining the use of these agents as anticonvulsants and anxiolytics.

NEUROPATHIC PAIN

Gabapentinoids are approved on the PBS for neuropathic pain refractory to other treatments and some people achieve a significant reduction in pain with these agents. However, many patients may find the agents have no benefit or adverse effects outweigh any benefit .

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system and can be further divided into central or peripheral neuropathic pain (see **Table 1**).

The efficacy of gabapentinoids for different types of pain is variable, with moderate efficacy for some forms of peripheral neuropathic pain and minimal or no efficacy for sciatica. A Cochrane review of pregabalin for neuropathic pain in adults was conducted in 2019,[10] and the National Institute for Health and Care Excellence in the United Kingdom reviewed the efficacy of pharmacological interventions for sciatica in 2020.[11] The efficacy of gabapentinoids specifically for sciatica was also reviewed in 2021.[12] The main findings of these studies are summarised in **Table 2** and indicate that gabapentinoids are no more effective than placebo for sciatica.

Central Neuropathic Pain	Peripheral Neuropathic Pain
Spinal cord or brain injury	Postherpetic neuralgia
Stroke	Trigeminal neuralgia
Multiple sclerosis	Radiculopathies (esp lumbar)
	Diabetic neuropathy

Table 1: Common types of Neuropathic Pain

FIBROMYALGIA

Fibromyalgia is a disorder associated with nociplastic pain. In such conditions pain is associated with activation of peripheral nociceptors caused by altered nociception in spite of no clear evidence of actual or threatened tissue damage. Pregabalin has been shown to be moderately effective in reducing pain intensity for a small proportion of people with fibromyalgia (9%). These results are similar for other medications used for fibromyalgia (see **Table 2**).[13,14]

OTHER CHRONIC PAIN CONDITIONS

Systematic reviews have found no treatment benefit for gabapentinoids over placebo for the management of low back pain,[15] spinal stenosis and episodic migraine. [16]

Type of Pain	Daily Dose of Gabapentinoid	Number of Studies	Efficacy of Gabapentinoid	
			Outcome Measure	Difference to Placebo (Number Needed to Treat)
Post-Herpetic Neuralgia	300mg Pregabalin	4	50% or greater reduction in pain intensity	19% (NNT = 5.3)
	600mg Pregabalin	4	50% or greater reduction in pain intensity	26% (NNT = 3.9)
Diabetic Neuropathy	300mg Pregabalin	8	50% or greater reduction in pain intensity	7% (NNT = 22)
	600mg Pregabalin	5	50% or greater reduction in pain intensity	13% (NNT = 7.8)
Mixed Neuropathic Pain	600mg Pregabalin	4	50% or greater reduction in pain intensity	14% (NNT = 7.2)
Central Neuropathic Pain	600mg Pregabalin	4	50% or greater reduction in pain intensity	11% (NNT = 9.8)
Sciatica	Pregabalin	4	Leg Pain	No Difference
		4	Back Pain	No Difference
		4	Disability	No Difference
Fibromyalgia	300-600mg Pregabalin	5	50% or greater reduction in pain intensity	9% (NNT=11)

Table 2: Efficacy of Pregabalin for Pain (adapted from Refs [10,11,12,13,14])

ADVERSE EFFECTS

As centrally acting agents, gabapentinoids should be used with caution in all people. Common dose-related adverse effects include[10,13,17]

- confusion, memory impairment,
- somnolence
- falls (dizziness, gait disturbance, ataxia and impaired balance)
- dry mouth
- weight gain and peripheral oedema
- euphoria

Whilst mental health comorbidities (especially depression and anxiety) are common in people with pain, there are case reports of worsening mood, depression and suicidal ideation affecting some patients soon after starting pregabalin.[18]

There are people at higher risk of adverse effects due to comorbidities or use of other centrally acting medications. Patients with pre-existing gait or CNS disorders, or heart failure are at increased risk of adverse effects.

The high renal clearance of gabapentinoids means that patients with renal impairment are at particularly high risk of accumulation and adverse effects. Only a modest degree of renal impairment warrants greater caution, with dose reduction recommended for gabapentin when creatinine clearance falls to 79mL/min and for pregabalin when creatinine clearance falls to 60mL/min. Combination use of gabapentinoids with opioids, benzodiazepines or illicit drugs is associated with an increased risk of toxicity and death.[19,20,21]

In a review of prescribing in Australian general practices, pregabalin was co-prescribed with an opioid in 38% of cases, with a benzodiazepine in 14% of cases and with both these agents in 4% of cases.[2]

MISUSE POTENTIAL

In addition to the risk of major adverse effects outlined above, there is increasing concern regarding the abuse and misuse of gabapentinoids. An international review of the literature identified almost 12000 reports of gabapentinoid misuse and dependence over the 11 years to 2015, 75% of which occurred in the most recent 3 years.[22]

A number of risk factors have been established for patients more likely to misuse gabapentinoids.[23,24] These include patients

- with a previous history of drug-seeking behaviour
- with a mental health disorder
- who are younger (<55years of age)
- who are male
- who are unemployed
- with a known substance use disorder
- using higher strengths of pregabalin.

FACTORS TO CONSIDER

FACTORS TO CONSIDER BEFORE DEPRESCRIBING

Gabapentinoids are moderately effective for neuropathic pain, with between one in 7 and one in 20 people with postherpetic neuralgia or diabetic neuropathy obtaining benefit. They are ineffective for sciatica and for non-neuropathic pain.

Determining that the pain has clear neuropathic features is an important first step in assessing the appropriateness of gabapentinoid prescribing, followed by ascertaining if the patient has obtained a clinically significant benefit, in terms of pain control, function and quality of life

The use of a questionnaire such as the DN4 may assist in clarifying signs and symptoms consistent with neuropathic pain. The National Prescribing Service also has resources demonstrating sensory tests that may be performed for patients with neuropathic pain presentations (comparing painful areas to non-painful sites/areas).

IN FAVOUR OF DEPRESCRIBING

- If there are no clear indicators of neuropathic pain the use of gabapentinoids is unlikely to provide benefit. A useful indicative examination finding is a decrease in sensation to touch and/or pinprick in the area of the pain.
- Gabapentinoids are ineffective for sciatica or low back pain. Patients prescribed gabapentinoids for these purposes are likely to benefit from dose reduction and eventual cessation, by eliminating the risk of developing adverse effects.
- Patients at high risk of misuse of gabapentinoids would benefit from alternative strategies for their neuropathic pain.
- Patients with overt adverse effects or on high doses of gabapentinoids may benefit from dose reduction, often resulting in similar benefit with a lower risk of adverse effects.
- Patients at increased risk of harm from gabapentinoid adverse effects (cognitively impaired, renal impairment, gait disorders, co-prescribed other CNS active agents) should have their use of gabapentinoids reviewed frequently with a view to dose minimisation or cessation.

AGAINST DEPRESCRIBING

- Beneficial short term response to postherpetic or diabetic neuropathic pain.

DISCONTINUATION SYNDROMES

Abruptly stopping gabapentinoids may result in withdrawal symptoms that include insomnia, nausea, headache, anxiety, sweating and diarrhoea. Most patients can have their gabapentinoids tapered over a week or two, however, slower tapering may reduce the severity of these discontinuation symptoms For patients who have been taking gabapentinoids long term (greater than 6 months) or at high doses, a tapering schedule over 4-8 weeks is preferable.

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