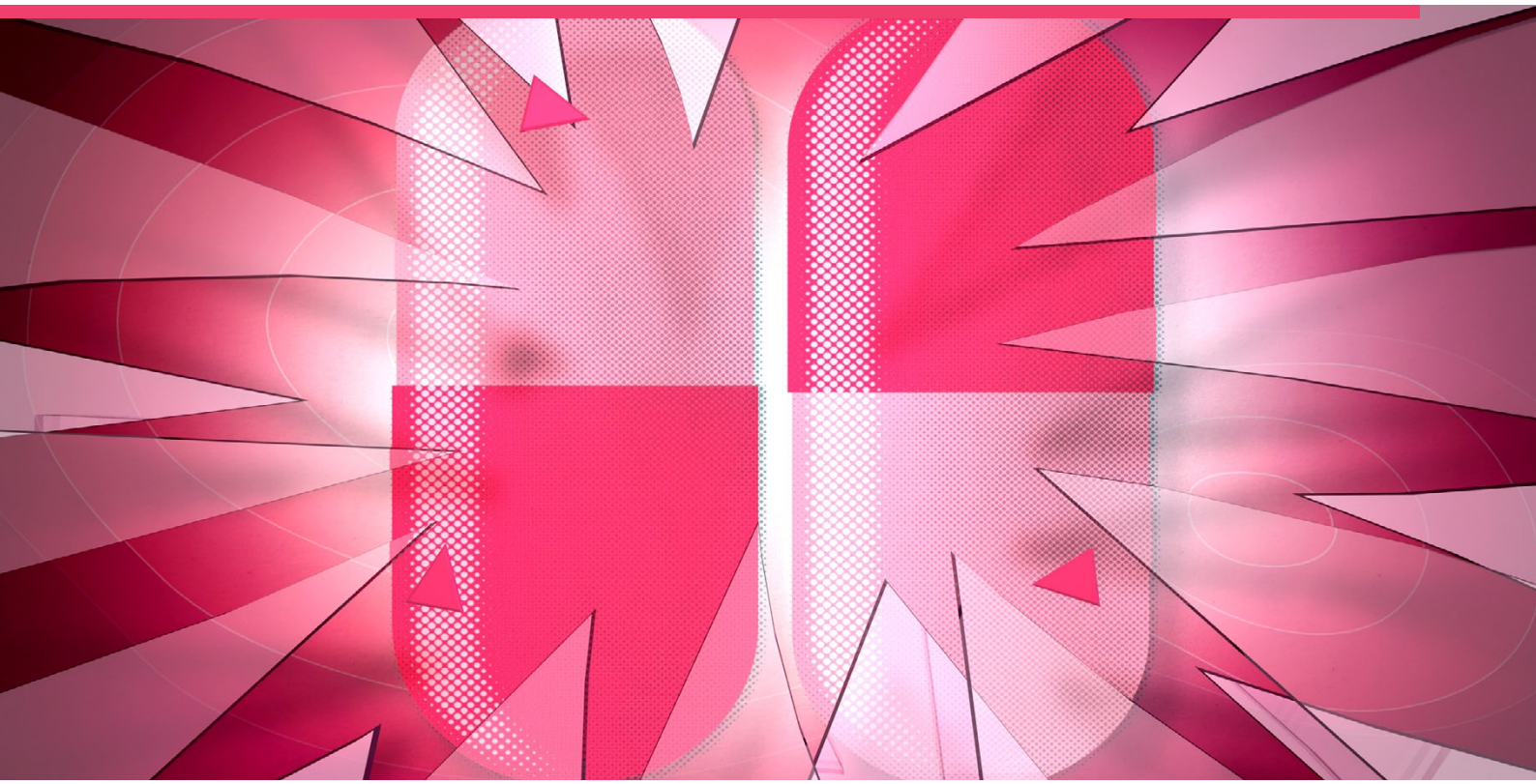

Prescribing gabapentin and pregabalin: upcoming subsidy changes

KEY PRACTICE POINTS:

- From 1 May, 2018, pregabalin will be fully subsidised without restriction; it was not previously subsidised
- From 1 June, 2018, Special Authority approval requirements will be removed from gabapentin and it will be fully subsidised without restriction
- Tricyclic antidepressants (TCAs), gabapentin and pregabalin are recommended first-line pharmacological treatments for patients with neuropathic pain
- There is no clear evidence that tricyclic antidepressants, gabapentin or pregabalin are more effective than each other for neuropathic pain
- Response to medicines for neuropathic pain is variable and patients may need to trial multiple medicines, doses and combinations to achieve a satisfactory regimen; in some cases all pharmacological options will be ineffective
- Gabapentin and pregabalin both have potential for misuse or diversion (on-selling); primary care health professionals should be alert for potential drug seeking behaviour

This article is an update to our 2016 article on managing neuropathic pain, focusing on the use of gabapentin and pregabalin, as subsidy changes will come into effect for these medicines in mid-2018. For further information on the diagnosis and full range of treatments for neuropathic pain, see: "Managing patients with neuropathic pain" **bpac.org.nz/BPJ/2016/May/pain.aspx**

From mid-2018 clinicians in primary care will have more prescribing options for patients with neuropathic pain

Tricyclic antidepressants (TCAs), gabapentin or pregabalin (see: "What is pregabalin") are recommended first-line medicines for patients with neuropathic pain.[1, 2 *] TCAs used to manage neuropathic pain, such as amitriptyline and nortriptyline, are fully subsidised without restriction. From 1 June, 2018, the requirement for Special Authority approval will be removed from gabapentin and it can be prescribed fully subsidised without restriction.[†] The subsidised brand of gabapentin will also change (see: "The subsidised brand of gabapentin is changing"). From 1 May, 2018, pregabalin can be prescribed fully subsidised without restriction[†]; it was not previously subsidised.

Topical capsaicin cream (0.075%) may be appropriate for patients with localised pain; it is subsidised if the prescription is endorsed, stating that it is for a patient with post-herpetic neuralgia or diabetic peripheral neuropathy. Opioids, such as tramadol or morphine, are second and third-line options for neuropathic pain as they are not as safe or effective as first-line options.[3]

* Carbamazepine is recommended as the first-line medicine for patients with trigeminal neuralgia[1, 2]

† Concurrent use of gabapentin and pregablin is not subsidised, i.e. only one medicine will be subsidised at a time

Setting realistic expectations for treatment with gabapentin or pregabalin for neuropathic pain

Gabapentin and pregabalin are not superior to TCAs for neuropathic pain: there is insufficient evidence to conclude that any of the first-line medicines are more effective than one another or provide better outcomes for patients with neuropathic pain.[2, 3]

Gabapentin and pregabalin are not recommended as general analgesics: they are not indicated, and have limited effectiveness, for the treatment of nociceptive pain without a neuropathic component, e.g. non-specific chronic low back pain.[5]

Medicines for managing neuropathic pain are modestly effective: randomised placebo controlled trials indicate that four to ten patients would need to be treated with a first-line medicine for neuropathic pain for three to 12 weeks for one patient to have a 50% reduction in pain, compared to no treatment (NNT = 4–10).[3] As pain reduction is a more realistic expectation than elimination of pain, patients can be encouraged to continue using a medicine if some benefit is gained, provided that adverse effects and other risks from treatment do not outweigh this benefit.

What is pregabalin?

As pregabalin has not previously been subsidised in New Zealand, it may be a new medicine for some prescribers. Like gabapentin, pregabalin was designed with the original therapeutic intent of managing seizures in patients with epilepsy, however, in clinical practice it is primarily used for managing neuropathic pain. Both medicines derived their names from their presumed action on the neurotransmitter gamma aminobutyric acid (GABA). However, research has subsequently found that they do not activate GABA receptors.[4] Some of their activity derives from activating pre-synaptic calcium channels that are widely distributed in the body, which reduces the release of several neurotransmitters, including glutamate, noradrenaline, serotonin and dopamine.[4] Pregabalin and gabapentin are often jointly referred to as gabapentinoids.[4]

The response to medicines for neuropathic pain is highly individual: patients may find they have little pain relief with one medicine but benefit from another, and a medicine that does not work well for one patient may be beneficial for another.[6]

It may take some time for medicines to be effective: a four to eight week trial, or longer, of treatment is appropriate before assessing whether a medicine for neuropathic pain has worked. This allows time for titrating to an optimum dose, and taking that dose for a sufficient duration.[7]

Consider adverse effects, interactions and co-morbidities to guide prescribing choices: also consider a patient's history of substance misuse; gabapentin and pregabalin have the potential to be misused for their euphoric effects (see: "Pregabalin and gabapentin have significant potential for misuse").

Prescribing gabapentin or pregabalin for neuropathic pain

Before prescribing gabapentin or pregabalin, consider the following points:

- Has a diagnosis of neuropathic pain been established? Characteristic sensory symptoms include burning, prickling or electric shock sensations and sensitivity to touch (allodynia). A questionnaire such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) can aid in diagnosis (link below).
- Is there an identifiable underlying cause to the pain that can be treated? e.g. nerve compression that may require surgery
- Have non-pharmacological treatments been discussed as part of the management plan? e.g. goal setting, pacing of activities, mindfulness and relaxation techniques
- Are there associated co-morbidities that also require management? e.g. depression, anxiety or insomnia
- Has a TCA, such as amitriptyline or nortriptyline, been considered? e.g. a TCA may be a good option for a patient with pain that is especially troublesome at night

Further information on diagnosing and managing neuropathic pain, including the LANSS, is available from: **https://bpac.org.nz/BPJ/2016/May/pain.aspx**

Information for patients about neuropathic pain is available from: **www.healthnavigator.org.nz/health-a-z/n/nerve-pain/**

Start with an analgesia plan

Whenever medicines are prescribed for pain, it is best practice to create an analgesia plan with the patient, which can be

discussed verbally and written down. A plan should provide the patient with clear instructions on how to use their medicines appropriately, including the dose and frequency, when or if they can increase the dose, common adverse effects and how to reduce the dose and stop medicines as their pain improves. Agree on a review schedule, e.g. seeing the patient again within two to four weeks of initiating a medicine or changing a dose, in order to assess the development of adverse effects and how well their pain is controlled.

An example of a pain management template is available from: **www.guild.org.au** search for "pain management plan"

Initiating and escalating doses

Gabapentin requires an initial slower titration than pregabalin to minimise the incidence of dose-related adverse effects, such as sedation and dizziness.[2] A dosing protocol is given in Table 1. However, for either medicine clinicians may prefer to use a much slower titration to a reach a dose that is maximally effective, while minimising adverse effects. Patients who are more susceptible to adverse effects, such as frail elderly people, may be started on lower doses than shown in Table 1, and titrated more gradually.[12] For example, initiate gabapentin 100 mg, once daily at night, increasing to 100 mg, twice daily, then 100 mg, three times daily. Some patients may require one week at each dose before increasing to the next.

Reduced doses are required in patients with renal impairment

Pregabalin and gabapentin are not metabolised to a significant extent and are excreted in the urine unchanged. They do not affect the metabolism of other medicines, such as oral contraceptives or anticonvulsants.[13] Reduced doses are required in patients with an eGFR ≤ 80 mL/minute/1.73m^2 for gabapentin or ≤ 60 mL/minute/1.73m^2 for pregabalin; refer to the NZF for specific dosing recommendations for patients with renal function below these thresholds: gabapentin – **www.nzf.org.nz/nzf_2629** pregabalin – **www.nzf.org.nz/nzf_2631**

The adverse effects of gabapentin and pregabalin

Adverse effects, such as sedation, increase in frequency with higher doses of gabapentin and pregabalin, and doses may need to be titrated up or down in order to find an acceptable balance between the analgesic effects and adverse effects of these medicines.[15]

Problems with balance and sedation are the most commonly reported adverse effects of gabapentin or pregabalin (Table 2). Up to one in three patients experience dizziness, and one in three, sedation.[16] Consider reducing doses or withdrawing these medicines if adverse effects are problematic. Tricyclic

Table 1: Dosing comparisons of gabapentin and pregabalin.[3, 13, 14]

	Gabapentin	Pregabalin
Initial dosing and titration	**EITHER:** Option 1: Increase by 300 mg each day ■ Day 1: 300 mg, once daily ■ Day 2: 300 mg, twice daily ■ Day 3: 300 mg, three times daily **OR:** Option 2: Start higher but increase slower ■ Day 1: 300 mg, three times daily ■ Every two to three days thereafter: increase by 300 mg, daily in three divided doses	Initially: 150 mg, daily in two divided doses After three to seven days: 300 mg, daily in two divided doses
Dose frequency after initial titration	Three times daily	Twice daily
Recommended dose range for patients with neuropathic pain	1200–3600 mg, daily	300–600 mg, daily
Bioavailability (fraction of dose absorbed)	**Non-linear:** Decreases as dose is increased; plasma concentrations do not increase proportionally with increasing dose	**Linear:** Constant at all doses; plasma concentrations increase in proportion to dosing, e.g. twice the dose results in twice the blood level

antidepressants also cause sedation, but they can be dosed once daily at night, therefore this may be a better option for some patients.

Weight gain is likely: Both gabapentin and pregabalin are associated with a variable amount of weight gain, which is dose dependent and typically occurs after three to 12 months of use. The majority of patients gain less than two kilograms, but up to 15% of patients, depending on dose, can gain over five kilograms.[17, 18] Encourage patients to follow recommendations for a healthy diet and exercise; maintaining activity should also be part of the non-pharmacological management strategy for neuropathic pain.

Changes in mood may occur: In clinical trials, 6% of patients taking pregabalin at therapeutic doses reported experiencing euphoria, and case reports suggest similar effects may occur in patients taking gabapentin (see: "Pregabalin and gabapentin have significant potential for misuse").[15, 19] Pregabalin and gabapentin are anti-epileptic medicines, and anti-epileptic medicines in general have been associated with a small increased risk of suicidal thoughts and behaviour, regardless of indication.[14] Patients should be encouraged to report any unusual changes in mood, including euphoria.

Respiratory depression is possible: Recent evidence shows that in rare cases gabapentin can cause respiratory depression.[20] Lower doses may be necessary in patients at increased risk of experiencing respiratory depression, including patients with respiratory or neurological disease, renal impairment, elderly people and those who are also taking other CNS depressants, such as opioids (see: "Caution is required if gabapentin or pregabalin are prescribed in combination with opioids").[21] Enquire at follow up appointments about breathing difficulties, shallow breathing or any other respiratory symptoms.[21]

Table 2: Common adverse effects in patients taking pregabalin or gabapentin.[15, 22, 23]

	Percentage of patients experiencing adverse effect
Dizziness/balance	19–31%
Sedation	14–29%
Dry mouth	15%
Weight gain	Up to 15% gain over 5 kg; see text for further details
Peripheral oedema	7%
Constipation	6%
Euphoria*	6%
Abnormal thinking	6%

For further information on adverse effects of gabapentin and pregabalin, refer to the NZF: **www.nzf.org.nz/nzf_2628**

* 6% of patients in clinical trials of pregabalin reported experiencing euphoria.[15] There are no similar clinical trial data for the incidence of euphoria when gabapentin is used as prescribed, however, both medicines are misused for their euphoric effects.[24] For further information, see: "Pregabalin and gabapentin have significant potential for misuse"

The subsidised brand of gabapentin is changing

Three brands of gabapentin are currently subsidised with Special Authority approval for patients with epilepsy, neuropathic pain or pruritus associated with stage five chronic kidney disease. From 1 June, 2018, a different brand of gabapentin will be subsidised, without restriction. All patients currently prescribed gabapentin will need to change to the newly subsidised brand by 1 November, 2018. Provided clinicians prescribe generically, i.e. writing/selecting "gabapentin" rather than a brand name, or checking the box to allow generic substitution on an electronic prescription, this brand change will be done by the pharmacist.

Approximately 1300 people in New Zealand are taking gabapentin for the management of epilepsy.[8] General practitioners do not need to notify the New Zealand Transport Association (NZTA) if patients using gabapentin for epilepsy change from one brand to another. Evidence suggests there is unlikely to be a change in seizure control and switching brands of gabapentin does not constitute a change in treatment for the purposes of driver licence assessment.[9, 10] Changes to the appearance of a medicine can influence adherence, so further support and discussion around these changes may be required for some patients.[11]

For further information on assisting patients with epilepsy with medicine adherence, see: **https://bpac.org.nz/2017/epilepsy.aspx**

Follow up patients to assess benefit

A follow-up appointment should be scheduled two to four weeks after initiating or increasing the dose of any analgesic for patients with neuropathic pain.[6] Most patients can be expected to have a small reduction in pain but are unlikely to be pain free. At least four to eight weeks of treatment with a first-line medicine is necessary for doses to be titrated and taken at a therapeutic level for a sufficient duration to assess efficacy.[7] Discuss the balance of benefit and adverse effects with patients and whether they regard the reduction in pain sufficient to continue using the medicine; this discussion can be regularly revisited if the medicine is continued.

A pain diary can help patients assess the effectiveness of an analgesic plan. A template is available from: **www.guild.org.au** search with "my pain diary"

Changing or combining medicines for neuropathic pain

Increasing the dose or switching to another first-line medicine for neuropathic pain may be appropriate for patients who experience a partial response but feel that the pain relief is still inadequate.[6] If a first-line medicine has not produced sufficient benefit, withdraw the medicine and initiate a different first-line medicine, e.g. a tricyclic antidepressant if gabapentin or pregabalin has been insufficient, or vice versa. Despite the fact that pregabalin and gabapentin have similar mechanisms of action, clinical experience suggests that patients who do not respond to one of these medicines may still derive benefit from the other.[27] If patients have not found any of the first-line medicines sufficiently beneficial, consider combination treatment with two first-line medicines (see below).

Gradual dose reduction over seven days is recommended when withdrawing patients from gabapentin or pregabalin as abrupt discontinuation can cause insomnia, nausea, sweating and anxiety; slower withdrawal may be necessary in some patients.[6] There is little evidence to help guide clinicians regarding appropriate strategies to switch patients between these medicines.[28] In some clinical trials, patients have abruptly stopped one medicine and started the other the following day without reporting adverse effects.[28] Alternatively, a slower process of switching could be carried out, such as halving the dose of the original medicine, and introducing the second at half the intended dose for the first few days, then stopping the original medicine and continuing treatment with the second at the full dose.[28]

A combination of first-line medicines may be trialled: Combining medicines with different mechanisms of action may provide patients with better analgesia than higher doses of a single medicine.[29] For example in one study, nortriptyline 50 mg, daily, with gabapentin 2000 mg, daily in divided doses, provided better pain relief than nortriptyline 60 mg, daily or gabapentin 2250 mg, daily alone. Although the combination of gabapentin with pregabalin is sometimes used in practice, there is little evidence to support this and subsidy is not available for both medicines concurrently.[9, 30]

Re-consider the diagnosis of neuropathic pain or consider whether an underlying condition is worsening if patients have trialled multiple first-line medicines without benefit.

Add opioids with caution

In some cases, first-line medicines will not be sufficient in patients with severe neuropathic pain and they will also require an opioid, e.g. tramadol or morphine. Gabapentin or pregabalin can be continued in patients prescribed opioids, however, caution is required as the combination of these medicines can increase the risk of potentially fatal adverse effects, such as respiratory and CNS depression. The risk of accidental overdose

Pregabalin and gabapentin have significant potential for misuse

Both gabapentin and pregabalin have the potential for misuse and diversion as recreational drugs.[25, 26] They are misused in order to produce euphoria, a state of relaxation and sociability or amplify the effects of other recreational drugs.[25] Reports suggest pregabalin may have a greater potential for misuse than gabapentin as it is more likely to produce euphoria and has greater bioavailability at high doses.[24] Clinicians and pharmacists should be alert for early requests for repeat prescriptions or consider whether patients may be obtaining prescriptions from multiple doctors. Establishing an appropriate analgesic plan with the patient prior to prescribing, including the expected duration of use, may help reduce the potential for misuse (see: "Create an analgesia plan with the patient").

For further information on identifying and managing drug seeking behaviour, see: **https://bpac.org.nz/BPJ/2008/September/misuse.asp**x

is also increased and the ability to perform tasks such as driving or operating machinery may be affected.[24]

Regularly consider the need for continued use of medicines

Although in many cases neuropathic pain is ongoing due to an underlying degenerative or non-treatable condition, in some cases medicines for neuropathic pain will be prescribed for a condition where improvement is possible or expected, e.g. post-herpetic neuralgia or post-surgery. Regular review of the ongoing need for analgesia is recommended. Expectations for duration of treatment and a plan for withdrawal of medicines are best set when treatment is first initiated.

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