



Question: What conversion ratio is recommended between pregabalin and gabapentin?

April 2019

Summary

- There is no established guidance on the conversion of gabapentin to pregabalin or vice versa. Thus, firm recommendations cannot be made.
- The product information for pregabalin and gabapentin suggest that both agents should be discontinued over the course of a week, although whether this is relevant for patients with neuropathic pain remains unclear.
- Very few studies have been published on the subject and those that are available have limitations including small study populations. Studies have used a pregabalin dose which is approximately one-sixth that of the gabapentin dose. However, this approach has not been proven by robust evidence and it is not widely used in practice.
- Any decisions regarding these conversions would need to be based on clinical judgement in partnership with the patient. Patients should be supervised closely during the conversion period.

Background

Although gabapentin and pregabalin were originally developed as antiepileptic drugs both are also licensed for the treatment of neuropathic pain.^{1,2}

The mechanism of action is similar for pregabalin and gabapentin. Both drugs bind to the $\alpha 2\delta$ subunit of voltage-gated calcium channels in the central nervous system.^{1,2,3,4} Gabapentin has nonlinear pharmacokinetics, meaning careful titration of dose is required, whereas pregabalin possesses linear pharmacokinetics, which means dosing regimens are more straightforward.^{3,4}

The individual Summary of Product Characteristics for both agents suggests gradual discontinuation over the course of a week.^{1,2,3} However, this withdrawal is to minimise the risk of increased seizure frequency where they are being used for patients with seizure disorders.³ The clinical importance of a slow withdrawal in patients with neuropathic pain remains unknown.³ Of note, other withdrawal symptoms have been reported with both agents including insomnia, headache, nausea, anxiety, diarrhoea, flu-like symptoms, pain, hyperhidrosis and dizziness, confusion, and palpitations.^{1,2,3} Thus, it would be prudent to consider gradual discontinuation. Any decisions made will need to be based on a clinical judgement, in partnership with the patient.

Starting Doses in Neuropathic Pain

The recommended starting dose of gabapentin is 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg three times a day on day 3.^{1,5} Lower doses should be used in older patients with renal impairment.¹ In practice, lower doses and slower titration of gabapentin is often considered. If necessary, the dose may be increased based on individual patient response and tolerability at intervals of 2-3 days.^{1,5}

The recommended starting dose of pregabalin is 150mg per day in 2-3 divided doses.^{2,6} Lower doses should be used in older patients with renal impairment.² In practice, pregabalin is often started at 25mg or 50mg at night in older patients. If necessary, the dose may be increased as tolerated, at intervals of 3-7 days.^{2,6}

Conversion Ratio

There is very limited evidence to guide the management of switching between the two agents. The maximum dose of gabapentin licensed to treat neuropathic pain is 3600mg per day in divided doses.^{1,5} The maximum dose of pregabalin used to treat neuropathic pain is 600mg per day in divided doses.^{2,6} Based on these maximum doses, Bockbrader NH et al conducted pharmacokinetic research comparing pregabalin and gabapentin in 2010, and again in 2013 which used an estimated potency difference between pregabalin and gabapentin of 6 to 1^{4,7}. Elsewhere, Toth et al have carried out research based on the assumption that pregabalin is six times more potent than gabapentin.⁸ Toth et al carried out a cohort study of 116 patients with peripheral neuropathy and neuropathic pain and assessed the outcomes of switching from pregabalin to gabapentin.⁸ The study results suggest that pregabalin may provide additional pain relief and improved quality of life than gabapentin, in those using these agents for peripheral neuropathy. Given that each of these studies involved small numbers of patients^{4,7,8}, this conversion ratio must be considered only to be approximate.

Dose substitution was carried out by Toth et al as follows⁸:

Daily Dose of Gabapentin Pre-Switch (mg/day)	Daily Dose of Pregabalin Post-Switch (mg/day) (Using Twice Daily Dosing)
0-900	150
901-1500	225
1501-2100	300
2101-2700	450
2700 or higher	600

Another small study of 32 patients with post-herpetic neuralgia examining the outcomes of changing from gabapentin to pregabalin was carried out by Ifuku et al.⁹ For the purpose of this study, patients were prescribed pregabalin at one-sixth the dosage of gabapentin and this was shown to be effective.⁹

Timing of Switch

In their cohort study Toth et al performed all substitutions using an overnight switch of the medications.⁸ Similarly, in Ifuku et al's research, gabapentin was substituted with pregabalin without any change to frequency of dosing.⁹ Bockbrader's pharmacokinetic simulation studies looked at two different gabapentin to pregabalin transition designs:^{4,7}

- The first design involved immediate discontinuation of gabapentin therapy with initiation of pregabalin therapy at the next scheduled dose period.⁷
- The second design featured a gradual cross-taper transition involving co-administration of 50% of the gabapentin dosage and 50% of the desired pregabalin dosage for 4 days, followed by discontinuation of gabapentin and fully targeted dosages of pregabalin.⁴

In both designs, transition from gabapentin to pregabalin was seamless, with predicted pregabalin-equivalent concentrations comparable following immediate discontinuation of gabapentin and the gradual discontinuation of gabapentin.

Another small study including 26 patients who were directly switched from gabapentin to pregabalin was presented as a conference abstract.³ Patients were switched directly to pregabalin after stopping gabapentin with no dose tapering or wash out period, with good effect.³ Yilmaz et al conducted a cross-over study design in which patients with neuropathic pain due to spinal cord injury were randomised into either the pregabalin or gabapentin group.³ A two week washout period was observed.³

The available data suggests that transitioning patients from gabapentin to pregabalin can be done using an overnight switch, or using a cross-taper approach. Based on ease of an overnight switch, this will be the best option in the case of most patients. Importantly, however, the efficacy and safety of these approaches has not been established.

References

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