



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

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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 they have limitations including small patient numbers. Studies have used a pregabalin dose which is approximately one-sixth that of the gabapentin dose. Therefore, gabapentin 300mg orally is equivalent to approximately pregabalin 50mg orally. However, this approach has not been proven by robust evidence and it is not widely used in practice at the moment.
- Any decisions made will need to be based on a clinical judgement, in partnership with the patient and the conversion should be carried out by a practitioner with experience of switching between gabapentin and pregabalin.

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 3 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. However, there are two small studies available that suggest a conversion ratio for switching between gabapentin and pregabalin.

The maximum dose of gabapentin used 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, Toth et al, assumed that pregabalin is six times more potent than gabapentin.⁷ However this assumption has not been proven by robust evidence. Toth et al carried out a cohort study of 116 patients with peripheral neuropathy and neuropathic pain assessed the outcomes of switching from pregabalin to gabapentin.⁷

Dose substitution was carried out as follows:

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

A second small study of 32 patients with post-herpetic neuralgia examined the outcomes of changing from gabapentin to pregabalin was carried out by Ifuku et al.⁸ Patients were prescribed pregabalin at one-sixth the dosage of gabapentin and this was shown to be effective.⁸

Timing of Switch

In their cohort study Toth et al performed all substitutions using an overnight switch of the medications.⁷ Similarly, Ifuku et al, gabapentin was substituted with pregabalin without any change to frequency of dosing.⁸

A pharmacokinetic simulation study looked at two different gabapentin to pregabalin transition designs.⁹

- The first design involved immediate discontinuation of gabapentin therapy with initiation of pregabalin therapy at the next scheduled dose period.⁹

- 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.⁹

In both designs, transition from gabapentin to pregabalin was seamless and rapid, with predicted pregabalin-equivalent concentrations highly comparable with plasma pregabalin concentrations within 1 day of pregabalin initiation in the immediate discontinuation model and within 1 day of gabapentin cessation in the gradual discontinuation model.⁹ This data suggests that transitioning patients from gabapentin to pregabalin could theoretically be achieved by either of the 2 approaches assessed.⁹ However, the efficacy and safety of these designs has not been established.

A small study included 26 patients who were directly switched from gabapentin to pregabalin presented as a conference abstract.³ Patients were switched directly to pregabalin after stopping gabapentin with no dose tapering or wash out period.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

References

1. Summary of Product Characteristics Neurontin 300mg Capsules. Available at www.hpra.ie. Accessed on the 28/11/2016.
2. Summary of Product Characteristics Lyrica Capsules. Available at www.medicines.ie. Accessed on the 28/11/2016.
3. UKMi. Q&A 408.3 'How do you switch between pregabalin and gabapentin for neuropathic pain, and vice versa?' March 2015. Available from www.sps.nhs.uk. Accessed on the 28/11/2016.
4. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N and Burger P. A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin. *Clinical Pharmacokinetics* 2010;49 (10): 661-669.
5. Monograph Gabapentin. British National Formulary. Available at www.medicinescomplete.com. Accessed on the 28/11/2016.
6. Monograph Pregabalin. British National Formulary. Available at www.medicinescomplete.com. Accessed on the 28/11/2016.

7. Toth et al. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. *Pain Medicine* 2010; 11: 456–465.
8. Ifuku et al. Replacement of gabapentin with pregabalin in postherpetic neuralgia therapy. *Pain Medicine* 2011; 12: 1112–1116.
9. Abstract only: Bockbrader HN, Budhwani MN, Wesche DL. Gabapentin to pregabalin therapy transition: a pharmacokinetic simulation. *American Journal of Therapeutics*. 2013; 20(1):32-6.