Switching from gabapentin to pregabalin

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Gabapentin and pregabalin are fully subsidised on prescription in New Zealand. Originally developed as anticonvulsants, they are more widely used for neuropathic pain. The proposed mechanism for analgesic activity is binding to the α2δ subunit of voltage-gated calcium channels in the central nervous system, which reduces the release of excitatory neurotransmitters such as glutamate.[1] Numbers needed to treat for 50% reduction in neuropathic pain are reported as 6.3 for gabapentin (5·0–8·3) and 7.7 for pregabalin (6.5–9.4), and are dose-related.[2] Switching from gabapentin to pregabalin may be considered for efficacy or tolerability reasons. Although there is no clear evidence that either gabapentin or pregabalin is more effective than the other for neuropathic pain,[1] patients may benefit from switching. In an open-label study, analgesia improved after switching from gabapentin to pregabalin.[3]

There is no established guidance on converting between gabapentin and pregabalin.[4] The manufacturers of both pregabalin and gabapentin advise that if they are to be stopped or changed to another medication, the dose should be tapered gradually over at least one week.[4] This gradual withdrawal is to minimise the risk of seizures where they are being used for patients with seizure disorders.[4] The importance of a slow withdrawal in patients with neuropathic pain remains unknown,[4] however discontinuation symptoms have been reported with abrupt cessation of both gabapentin and pregabalin. Discontinuation symptoms reported include insomnia, nausea, anxiety, pain, and sweating.[4] Determining dose equivalence between gabapentin and pregabalin is complicated by gabapentin's nonlinear bioavailability, in contrast to pregabalin's linear bioavailability.[6] Gabapentin's bioavailability ranges from 80% with 100mg tds[6] to 35% with 1,200mg tds.[7] Despite this, most published guidance on switching uses the same conversion ratio across gabapentin's dose range.[8,9] This risks giving too much pregabalin when converting from the higher end of gabapentin's dose range. The conversion ratio used in one study was "of the author's creation"[3] and in another study the authors assumed that pregabalin had six times greater pharmacological effect against neuropathic pain than gabapentin based on the maximum dose of each medicine.[8] Bockbrader et al[5] derived a potency ratio from EC50 data in post-herpetic neuralgia, which reflects the pharmacological activity of the two medicines.

Actual and modelled bioavailability data[6,7] were used to calculate the approximate amount of gabapentin absorbed, then Bockbrader's potency ratio[5] and a correction factor for pregabalin's bioavailability (90%)[1] were applied to develop a conversion algorithm:

Table 1: Proposed switching doses.

Gabapentin dose	Suggested dose of pregabalin
100mg tds	50mg bd
200mg tds	75mg bd
300mg tds	100mg bd
400mg tds	125mg bd
500mg tds	150mg bd
600mg tds	150mg m and 175mg n
700mg tds	175mg bd OR 175mg m and 200mg n
800mg tds	200mg bd
900mg tds	200mg m and 225mg n
1,000mg tds	225mg bd
1,100mg tds	225mg m and 250mg n
1,200mg tds	250mg bd
1,600mg tds	300mg bd

Pregabalin is available as capsules of 25mg, 75mg and 150mg in New Zealand.

If analgesic effect is suboptimal 1–2 weeks after completing the switch, pregabalin can be titrated up at seven-day intervals to a maximum daily dose of 300mg bd.[10]

As expected, pregabalin doses at the higher end of the dose range are more conservative than other published algorithms.[3,9]

Options for switching

There are three approaches described in the literature:

1. Stop/start: Take the last dose of gabapentin at night and start the target dose of pregabalin the following day. Two papers utilising this approach reported that it was effective and well-tolerated.[3,8]
2. Cross-taper: A pharmacokinetic simulation model compared a stop/start approach with a four-day cross-taper whereby 50% of the gabapentin dose and 50% of the target pregabalin dose is given for four days, followed by discontinuation of gabapentin and use of target dose of pregabalin.[5] Both approaches were pharmacokinetically comparable.
3. Taper down and stop gabapentin then gradually titrate pregabalin up: This is the approach recommended by the manufacturers. A gradual reduction may be more likely to avoid withdrawal symptoms. The main problem with this approach is possible loss of analgesic effect during the tapering down and titrating up phases.

The adverse consequences of giving too much pregabalin when switching from gabapentin are an increase in the intensity of side effects. Many patients are reluctant to continue a medicine if they have unpleasant side effects when starting treatment. Treatment choices in neuropathic pain are limited, so losing an option due to potentially avoidable side effects can be frustrating. Ifuku et al[8] reported a significant increase in the number of patients with peripheral oedema after switching from gabapentin to pregabalin.

The starting dose of pregabalin 75mg bd recommended by the manufacturer seems to have been too high for some of our patients started on pregabalin de novo (not switching) and they have described unpleasant cognitive side effects including dysphoria, feeling “spaced out” or “out of it”, excessive sedation and dizziness. We are now recommending a lower starting dose of 75mg at night, or 25–50mg in people who may be susceptible to adverse effects, eg, adults over 75 years old.[11] This is consistent with recommendations for both gabapentin and pregabalin to consider lower starting doses and/or slower titration in patients who may be more susceptible to adverse effects (such as frail elderly).[10] The dose of pregabalin should be reduced in renal impairment (eGFR ≤60ml/min).[10]

Competing interests:
Nil.

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