



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Gabapentin and pregabalin: Are high doses justified?

**A**nalgesia once seemed a relatively straightforward aspect of medicine. Recommendations in textbooks and guidelines were definitive, albeit heavily conflicted. Even recent guidelines encourage dose titration, based on an implicit, if unsupported, notion that more is likely to be better.<sup>1</sup>

Recent experiments and systematic reviews show that drugs seldom outperform placebo significantly in chronic pain. Even old standards like acetaminophen and amitriptyline do not stand up well to careful scrutiny of randomized placebo-controlled trials.<sup>2,3</sup> Recent evidence confirms that gabapentin and pregabalin are not useful for back pain or sciatica.<sup>4,5</sup>

“Pushing the dose” can be expensive and dangerous. It might be warranted if it led to better outcomes, but should be discouraged if it increases harms. Gabapentin and pregabalin are drugs of potential abuse. Pregabalin is a controlled drug in the US, gabapentin is controlled in some states and both will become controlled drugs in Great Britain in April 2019. **Both Health Canada and the UK government have warned that gabapentin can cause severe respiratory depression**, even without concomitant opioids.<sup>6,7,8</sup>

Almost all prescriptions for gabapentin and pregabalin in British Columbia are for chronic pain. In 2009 Therapeutics Letter 75 concluded that roughly equal numbers of people are harmed or benefit from gabapentin for classical neuropathic pain, e.g. post-herpetic neuralgia or painful diabetic neuropathy. Within 2 days of taking gabapentin 100-900 mg/day, patients can test for net benefit. At best 1 in 6 will be impressed. Higher doses or longer treatment are seldom warranted.<sup>9</sup> Similarly, in 2015 Therapeutics Letter 96 concluded that fewer than 1 in 10 people treated with pregabalin, venlafaxine, or duloxetine experience a meaningful decrease in pain. Higher doses increase harms without better analgesia.<sup>10</sup> Such conclusions are no longer radical.<sup>11</sup>



In 2016 over 111,000 British Columbians were prescribed gabapentin, including 29% at doses >1200mg/day and 19% at >1800mg/day. Nearly 29,000 received pregabalin, including 5% at >600mg/day.<sup>12</sup> This Letter focuses on dose-response analyses from randomized placebo-controlled trials (RCTs) of gabapentin and pregabalin in neuropathic pain.

We evaluated meta-analyses of RCTs included in three Cochrane reviews comparing fixed or flexible doses with placebo for chronic neuropathic pain.<sup>13,14,15</sup> All utilized a numeric rating scale (NRS) of 0-10 (or equivalent) to evaluate pain. Only 1 of 8 gabapentin studies and 1 of 14 pregabalin studies demonstrated an average improvement over placebo of 2 points for the 11-point NRS.<sup>16,17</sup> For individual patients, a 2-point difference in NRS rating could represent a minimal clinically important difference.<sup>18</sup>

### Higher doses increase harms

Both gabapentin and pregabalin increase adverse events versus placebo. This is consistently dose-dependent.<sup>14,17,19</sup> Gabapentin's most common adverse events are dizziness, somnolence, confusion, ataxia, lightheadedness, lethargy, and edema. Pregabalin increases somnolence, dizziness, ataxia, weight-gain, peripheral edema, blurred vision, diplopia, and headache.



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## Higher doses do not increase meaningful pain relief

**Gabapentin:** We assessed eight published RCTs comparing gabapentin with placebo over 4-8 weeks. Five trials used *forced titration*, and three flexible titration. *Forced titration* patients were pushed to daily doses of 1800 mg or 2400 mg. In the only published study that directly compared 1800 mg/day versus 2400 mg/day, the higher dose did not achieve a clinically meaningful reduction in pain. A large unpublished study in painful diabetic neuropathy found no difference from placebo in mean pain scores at doses of 900, 1200 or 1800 mg/day. No dose-response was found.<sup>20</sup>

In *flexible titration* trials, gabapentin doses ranged from 400-3600 mg/day. In one *flexible titration* trial patients in the gabapentin arm took a median dose of 2400 mg/day, but gabapentin doses above 1200 mg/day did not improve analgesia.<sup>21</sup>

**Pregabalin:** We evaluated fourteen RCTs comparing pregabalin with placebo over 4-16 weeks. Nine *forced titration* studies used daily doses of 150 mg, 300 mg, 450 mg or 600 mg. Daily doses above 300 mg did not decrease mean pain score more than lower doses.

Of five *flexible titration* trials, four used daily pregabalin doses between 150-600 mg; a fifth RCT used 300-450 mg/day.<sup>22-26</sup> Mean final daily doses of pregabalin were 400-500 mg. One trial reported no improvement in pain relief at doses >300 mg. The other four trials did not report data in a way to allow dose comparisons.

## Limitations

Randomized trials generally enrolled “ideal” patients without clinical conditions that may increase adverse effects or reduce efficacy, such as impaired kidney function, balance or frailty. Both drugs are excreted in the urine. For pregabalin, discontinuation for adverse effects was more common in people with reduced glomerular filtration rate and the same can be expected from gabapentin. People who had previously tried these drugs without relief were excluded. These and other important biases mean that RCT results represent the best case for benefits and harms, exaggerating what can be expected in the real world.

## Clinical considerations

The short elimination half-lives of gabapentin and pregabalin mean that people with normal kidney function reach steady-state within 1-2 days at any dose. Both drugs can be titrated at intervals of a few days to a week, based on pain response and tolerability. For patients wishing to try gabapentin, 300-900 mg/day is a reasonable starting point, but significant toxicity has been reported with doses as low as 100 mg/day. When there is no clinically meaningful decrease in pain, “pushing the dose” is not rational. Pregabalin doses as low as 50-100 mg/day also cause intolerable adverse effects for some. If useful relief is not achieved at modest doses, higher doses are equally unreasonable. **Generally, it makes little clinical sense to exceed 1800 mg/day of gabapentin or 300 mg/day of pregabalin.**

If a patient does improve, use the lowest effective dose. Remember that many painful conditions improve spontaneously over time. Reassess therapy regularly, given the lack of long-term data to support ongoing treatment. New health issues can make patients more vulnerable to impaired balance or mental status changes.

## Deprescribing

Tapering over a few days or weeks may avoid potentially significant withdrawal symptoms such as diaphoresis, anxiety, palpitations, confusion.<sup>27,28</sup> Dangerous adverse effects (e.g. falls, severe cognitive impairment, sedation or edema) require abrupt deprescribing.

## Conclusions

- Many British Columbians receive very high doses, against best evidence.
- **Most patients will not benefit from gabapentin or pregabalin for pain.**
- **Do not expect better pain relief from high doses.**
- At any dose, assess for benefit or harm within 1-2 weeks; reassess often for dose reduction or deprescribing.
- **Adverse effects increase at higher doses.** Expect more harms in frailty, impaired kidney function, or in patients using other sedative drugs or alcohol.

For the complete list of references go to: [www.ti.ubc.ca/letter117](http://www.ti.ubc.ca/letter117)

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