Pregabalin for Neuropathic Pain

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Unlike nociceptive pain, which is caused by noxious stimulation of pain fibres, neuropathic pain arises from damage or dysfunction of the nervous system (peripheral or central) itself (Table 1). Neuropathic pain is typically described with adjectives such as burning, tingling, or shock-like. Physical exam findings can include hyperalgesia and/or allodynia which may not respect dermatomal boundaries. Up to 3% of the population suffer from chronic neuropathic pain secondary to conditions such as diabetic neuropathy, post-herpetic neuralgia, sciatica or post-stroke pain syndrome.

Neuropathic pain can be challenging to treat and does not respond as well as nociceptive pain to standard non-opioid and opioid analgesic medications. Adjuvant analgesics are therefore considered first-line treatment for chronic neuropathic pain. A variety of medications have been shown to be effective in treating neuropathic pain (Table 2), with many more drugs currently under development. Tricyclic antidepressants remain the best-studied and most effective class of drug for this condition (number needed to treat to achieve > 50% pain reduction is approximately three).^1 A recently published review^1 and Canadian consensus statement provide helpful guidelines for treating this challenging condition.

Alan’s case

Alan developed a painful vesicular rash in the left T5 dermatome 3 months ago. Herpes zoster was promptly diagnosed and appropriate antiviral treatment provided.

The rash resolved, but a constant 8/10 burning pain over a wide area of his left chest wall persists. On examination, you find hyperalgesia and allodynia involving the T4, T5 and T6 dermatomes.

Past medical history is significant only for benign prostatic hypertrophy for which he takes an α-reductase inhibitor. He has supplemental health insurance providing drug coverage.

Concerned about the anticholinergic effects of tricyclic antidepressants in the context of benign prostatic hyperplasia (BPH), you decide to prescribe an anticonvulsant. Because it is easier to titrate than gabapentin, you choose pregabalin starting at 50 mg b.i.d. In 1 month, Alan’s dose has increased to 150 mg b.i.d. and his pain rating is 5/10. After another month, Alan’s pain is 3/10 and the hyperalgesia and allodynia are minimal.

Turn to page 72 for another case.

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Practical approach

Pregabalin vs. gabapentin

The use of adjuvant analgesics for pain is typically “off-label” since they have not been approved for this indication by Health Canada. Pregabalin is the first “adjuvant” analgesic whose primary indication is treatment of neuropathic pain. But is pregabalin really unique? Is it more effective, safer, easier to use or less expensive than current alternatives? Pregabalin’s closest comparator is gabapentin, an anticonvulsant that has been increasingly used for neuropathic pain in recent years.

Gabapentin and pregabalin share an identical mechanism of action. Both drugs suppress depolarization of afferent pain neurons by inhibiting calcium influx through voltage-gated calcium channels in the spinal cord. Both medications have proven efficacy for neuropathic pain arising from diabetic neuropathy and postherpetic neuralgia in multiple, well-designed, randomized, placebo-controlled clinical trials. While there have been no head-to-head comparisons, the published trials demonstrate that the number needed to treat to achieve a 50% reduction in pain intensity is similar for the two medications (approximately four).

Adverse effects for the two medications are similar, with dizziness and somnolence at the top of the list. Peripheral edema has been noted in approximately 10% of patients who take pregabalin. Both medications require dose adjustment in advanced renal failure.

Practical issues

Both gabapentin and pregabalin require titration to clinical effect over a wide therapeutic dose range. Pregabalin is initiated at 25 mg or 50 mg b.i.d., with an analgesic dose range from

Table 1

A pain glossary

- **Nociceptive pain**: pain caused by noxious stimulation of afferent pain fibres (nociceptors)
- **Neuropathic pain**: pain caused by damage or dysfunction of the central or peripheral nervous system
- **Hyperalgesia**: severity of pain perceived is out of proportion to the intensity of the noxious stimulus (e.g., severe pain arising from small pinprick)
- **Allodynia**: normally non-noxious stimuli are perceived as painful (e.g., pain caused by light touch)
- **Adjuvant analgesic**: a medication with another primary indication which has analgesic properties (e.g., tricyclic antidepressant for neuropathic pain)

Mary’s case

Mary, 72, has Type 2 diabetes, congestive heart failure and painful neuropathy in both feet. She describes unremitting 4/10 tingling discomfort in both feet. She finds acetaminophen with codeine ineffective.

Mary received pregabalin samples at a walk-in clinic, but wants to check with you before taking them. Her medications include metformin, glyburide, hydrochlorothiazide, an ACE inhibitor and a statin.

Examination reveals stable 2+ pitting edema in both feet with decreased vibration and light touch sensation. Skin is healthy and peripheral pulses are palpable.

Because pregabalin may exacerbate peripheral edema, you counsel Mary against using this medication for her painful neuropathy. Instead, you prescribe a quaternary-amine tricyclic antidepressant (TCA) (e.g., nortriptyline) as it carries less risk of anticholinergic effects than tertiary-amine TCAs (e.g., amitriptyline, imipramine). You explain that the analgesic benefits will take weeks to manifest and that gradual titration will be necessary. Eight weeks later, Mary is very pleased with the improvement in her symptoms.
100 to 300 mg q.d., divided b.i.d. (the maximum recommended daily dose is 600 mg q.d., but clinical trials have not demonstrated a dose-related benefit above 300 mg q.d.). For gabapentin, the starting dose is 100 to 300 mg q.d. Gradual titration is required toward the typical therapeutic range of 1,800 mg to 3,600 mg q.d., divided t.i.d. One significant advantage of pregabalin over gabapentin is ease of administration. Once a therapeutic dose is achieved, gabapentin requires more pills, more often (three to six capsules t.i.d.) than pregabalin (one capsule twice daily).

Provincial formulary coverage is another practical concern. Gabapentin enjoys unrestricted coverage in five provinces (British Columbia, Alberta, Saskatchewan, Manitoba and Quebec), while pregabalin is covered only in Quebec.

**Conclusion**

Neuropathic pain is a common condition that can prove frustrating for both patients and clinicians. Pregabalin provides a new therapeutic option and is similar in efficacy to existing first-line alternatives. As pregabalin and gabapentin have similar mechanisms of action, tolerability profiles and efficacy for neuropathic pain, it is often practical considerations (familiarity, cost, ease of administration, etc.) that become determining factors in choosing between the two agents.

**Table 2**

Pharmacologic options for neuropathic pain

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<td>Tricyclic antidepressants</td>
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<tr>
<td>Gabapentin</td>
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<td>Pregabalin</td>
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<td>Carbamazepine (only for trigeminal neuralgia)</td>
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<th>Second-line</th>
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<td>Venlafaxine</td>
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<td>Topical lidocaine 5%</td>
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<td>Tramadol</td>
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<td>Controlled-release opioids</td>
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**Frequently Asked Questions**

1. **Is there any point in trying someone on pregabalin who has not responded to gabapentin?**

   Maybe. No clinical trial has looked specifically at gabapentin non-responders, but some of the positive trials included patients who had previously been on gabapentin, so it may be worth a try.

**Take-home message**

- Tricyclic antidepressants, gabapentin and pregabalin are first-line options for treatment of neuropathic pain
- Pregabalin is more expensive than gabapentin, but is easier to titrate and requires fewer pills at typical analgesic doses

**References**