Pregabalin

Another option for neuropathic pain

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The long-awaited listing of pregabalin on the PBS for treatment of 'neuropathic pain refractory to treatment with other drugs' took place in March. Was it worth the wait?

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On 1 March 2013, the analgesic and anticonvulsant pregabalin was listed on the PBS for the treatment of 'neuropathic pain refractory to treatment with other drugs'.[1] This listing was long awaited by consumers and the pain management community as access to this drug was restricted largely because of cost. But what is the place of pregabalin in the treatment of neuropathic pain? This article will highlight the issues.

Chronic pain affects 20% of Australians and costs the economy 35 billion dollars a year, with neuropathic pain – defined as 'pain caused by a lesion or disease of the somatosensory nervous system' – being a major contributor.[2,3] Pregabalin was first approved by the TGA for the treatment of neuropathic pain in adults in April 2005.

PHARMACOLOGY OF PREGABALIN

Pregabalin binds to a subunit (the alpha$_2$-delta protein) of calcium channels found on neurons in the central nervous system, inhibiting release of excitatory neurotransmitters such as glutamate, particularly in the dorsal horn of the spinal cord. As a consequence, pregabalin has analgesic, anticonvulsant, anxiolytic, mood-stabilising and hypnotic properties.

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The pharmacokinetics of pregabalin determine many of its properties. In particular, pregabalin accumulates in patients with renal impairment (Table 1).[4]

CLINICAL USE IN PAIN MANAGEMENT

Pregabalin is similar to gabapentin in its actions and is the most studied drug for the treatment of neuropathic pain. Pregabalin is effective in postherpetic neuralgia, painful diabetic peripheral neuropathy and spinal cord injury pain. Patients often report improvements not only in pain but also in sleep and overall quality of life. On average, most healthy adults need a dosage of at least 300 mg pregabalin per day for a therapeutic effect. There are no

TABLE 1. RELATION BETWEEN PHARMACOKINETIC AND THERAPEUTIC EFFECTS OF PREGABALIN[4]

Pharmacokinetics	Therapeutic effect
High bioavailability (90%)	Absorption not affected by food
Rapid peak uptake (1 hour)	Rapid oral absorption
'Linear' uptake kinetics	Reliable dose titration
Elimination half-life, 6 hours	Twice daily dosing
Time to steady-state concentration, one to two days	Dose titration possible every two to four days
Minimal liver metabolism	No dose adjustment needed with liver dysfunction
Renal excretion, 98% (unchanged)	Accumulates in renal impairment, dose adjustment needed

head-to-head studies comparing pregabalin with other drugs for neuropathic pain, but indirect comparisons suggest similar efficacy and side effects (Table 2).[5-7] There is limited evidence that combining pregabalin with other drugs (e.g. pregabalin and morphine, or pregabalin and venlafaxine) may be therapeutic.

Treatment recommendations for neuropathic pain based on international and Australian guidelines are shown in the box on this page.[5-9] Pregabalin and gabapentin should be prescribed when tricyclic antidepressants or serotonin and noradrenaline reuptake inhibitors are ineffective, poorly tolerated or contraindicated. Opioids are also effective for neuropathic pain, but concerns about adverse effects have relegated them to second- or third-line treatments in most guidelines.

Pregabalin is also beneficial in fibromyalgia, acute postsurgical pain, prevention of chronic postsurgical pain and restless legs syndrome; use in these conditions is off-label (Table 3).[7-13] It has been trialled in lumbar radicular pain and low back pain (equivocal benefit), phantom limb pain (equivocal benefit), chronic migraine (low-quality studies suggest benefit) and irritable bowel syndrome (analgesia in experimental studies).

ADVERSE EFFECTS

In general, pregabalin is well tolerated, and most side effects are dose-dependent (Table 4). Dizziness and drowsiness are common (one-third of patients) and the main reason for ceasing treatment. Patients with diabetes and heart failure should be warned about peripheral oedema and weight gain. Patients at risk of renal impairment (e.g. those with diabetes) should have their serum creatinine level and estimated glomerular filtration rate measured before starting pregabalin. Patients with depression, anxiety or psychosis should be warned about worsening symptoms and, in rare cases, increased suicide risk. Patients should be warned not to cease pregabalin abruptly as this may lead to discontinuation syndrome. Apart from monitoring of renal function in certain patients, routine blood tests are not required with pregabalin.[4,5]

ADMINISTRATION

In Australia, pregabalin is available as 25, 75, 150 and 300 mg capsules. It is taken orally once or twice a day, with or without food.[4] Suggested starting doses (subject to current product information) are:[4]

- pregabalin 25 to 50 mg at night (up to twice daily if needed) in elderly or frail patients or those with renal impairment
- pregabalin 75 to 150 mg at night (up to twice daily if needed) in healthy adults.

The maximum dose in healthy adults is pregabalin 300 mg twice daily.

PRESCRIBING TIPS

- Remember that a PBS streamlined authority (code 4172) allows medical

TABLE 2. COMPARISON OF DRUGS USED FOR NEUROPATHIC PAIN CONDITIONS[5-7]

Drug	Number needed to treat*	Number needed to harm†
Pregabalin	5	11
Tricyclic antidepressants	3	16
SNRIs	5	13
Tramadol	5	13
Opioids	2	17

ABBREVIATION: SNRI=serotonin and noradrenaline reuptake inhibitor.
* Number needed to treat for a 50% reduction in pain in one person.
† Number who need to be exposed to the drug to cause harm in one person, with harm defined as the need to stop taking the drug.

DRUG TREATMENTS FOR NEUROPATHIC PAIN*[5-9]

First-line

- Tricyclic antidepressants (nortriptyline, amitriptyline, imipramine) or
- Serotonin and noradrenaline reuptake inhibitors (duloxetine, venlafaxine) or
- 'Gabanoids' (pregabalin, gabapentin) and/or
- Tramadol
- Carbamazepine (only for trigeminal neuralgia)

Second-line

- Opioids (buprenorphine patch, controlled-release oxycodone, methadone, morphine)

* Many of these drugs are used off-label for neuropathic pain (duloxetine is TGA approved for treatment of painful diabetic peripheral neuropathy).

TABLE 3. PREGABALIN IN PAIN MANAGEMENT[7-13]

Condition	NNT*	Level of evidence†	Comments
Peripheral neuropathic pain (PHN, PDPN)	4	I	↑ sleep, QoL
Spinal cord injury pain	6	II	↑ sleep, QoL
Fibromyalgia‡	10	I	↑ sleep, QoL
Restless legs syndrome‡	B	II	↑ sleep
Postsurgical pain (acute and chronic)‡	B	I	

ABBREVIATIONS: B=beneficial; NNT=number needed to treat; PDPN=painful diabetic peripheral neuropathy; PHN=postherpetic neuralgia; QoL=quality of life.
* Approximate number needed to treat for a 50% reduction in pain in one person.
† NHMRC level of evidence.
‡ Off-label use.

TABLE 4. POTENTIAL PROBLEMS WITH PREGABALIN[4,5]

Problem	Presentation and comments	Action
Common side effects	Dizziness, drowsiness, cognitive dysfunction, fatigue, falls risk	Adjust dose
Occasional side effects	Peripheral oedema, weight gain, visual disturbance, dry mouth, headaches, constipation, tremors, sexual dysfunction	Adjust dose
Rare side effects	Allergic reactions, congestive cardiac failure, rhabdomyolysis, hypoglycaemia, hyponatraemia, thrombocytopenia, neutropenia	Monitor clinically and with blood tests
Psychiatric effects	Increased suicide risk, worsening depression, anxiety and psychosis	Warn patients and carers
Neuroexcitation	Myoclonus, tremor, eye twitching, hyperacusis, seizures (usually with high doses or accumulation in renal impairment)	Avoid high doses, especially with renal impairment
Discontinuation syndrome	Agitation, confusion, anxiety, depression, tremor, headaches, nausea, diarrhoea, sweating, tachycardia, seizures (similar to opioid or benzodiazepine withdrawal or 'cold turkey')	Reduce dose slowly over at least a week
Abuse and dependence	Low risk (S4) but possible owing to psychoactive effects	Assess risk, monitor
Sedation	Increased sedation with alcohol, benzodiazepines, opioids	Avoid mixing with other sedatives
Special circumstances		
Renal impairment	Pregabalin will accumulate	Reduce dose; check product information in dialysis[4]
Pregnancy, breastfeeding	Pregnancy category B3	Avoid and cease
Children and adolescents	Not licensed for use in patients under 18 years of age	Seek specialist advice

and nurse practitioners to prescribe 56 capsules and five repeats for the treatment of 'neuropathic pain refractory to treatment with other drugs'.[1]

- Consider whether the patient has any contraindications to pregabalin.
- Consider renal function.
- Give the patient a consumer medicine information leaflet.
- Discuss adverse effects with the patient: dizziness, drowsiness, cognitive impairment, falls risk, weight gain, oedema, muscle aches, driving and workplace safety, suicide risk (where appropriate) and allergy.
- Warn patient not to cease pregabalin suddenly without medical advice
- 'Start low and go slow' with dosing, especially in elderly or frail patients or those with renal impairment.
- Make any dose changes at night first.
- Titrate dose up to every four days if needed, depending on clinical effects.
- Regularly assess therapeutic outcomes and cease pregabalin if there is no clear benefit.

KEY MESSAGES

- Pregabalin has analgesic, anti-convulsant, anxiolytic, mood-stabilising and hypnotic properties.
- Pregabalin is PBS authorised (streamlined authority code 4172) for 'neuropathic pain refractory to treatment with other drugs'.
- There are no major advantages or disadvantages to using pregabalin for neuropathic pain compared with tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors or tramadol.
- Pregabalin accumulates in patients with renal impairment.
- Mental state and suicide risk should be monitored in 'at risk' patients.
- Dose titration should 'start low and go slow', especially in the elderly.
- Most healthy adults need a dosage of at least 300 mg pregabalin per day for a therapeutic effect in pain management. MT

REFERENCES

A list of references is included in the website version (http://www.medicinetoday.com.au) and the iPad app version of this article.

This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

COMPETING INTERESTS: Dr Visser has received honoraria from Pfizer, Mundipharma and Janssen.

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