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Gabapentinoids

Gabapentinoids are a class of medicines indicated as an anticonvulsant for focal (partial) seizures and for neuropathic pain. These medicines are also prescribed off-label for a wide range of other conditions including migraine, low back pain, sciatica, alcohol use disorder, insomnia, anxiety, restless legs syndrome, chronic cough and bipolar disorder.

In Australia, the use of gabapentinoids has increased significantly since their approval over 20 years ago. Potentially inappropriate prescribing of gabapentinoids is common in Australian residential aged care facilities.

Pregabalin (*Lyrica*) is indicated on the PBS for neuropathic pain, refractory to treatment with other drugs. Gabapentin (*Neurontin*) is approved for the PBS for partial epileptic seizures and refractory neuropathic pain.

Dose

Pregabalin has higher potency, greater bioavailability and quicker absorption compared with gabapentin.

Gabapentin for epilepsy or neuropathic pain should be commenced at a dose of 300mg three times daily, increasing in increments of 300 to 400mg three times a day, up to a maximum of 2400mg a day. It is recommended that the time between doses not exceed twelve hours.

The dose of pregabalin when prescribed for epilepsy or neuropathic pain is initially 75mg twice daily, increasing after one week to 150mg twice daily. The maximum recommended dose is 300mg twice daily.

Off-label use of pregabalin for fibromyalgia treatment is recommended at a starting dose of 75mg twice daily, increasing to a maximum of 225mg twice daily if required.

Effective antiepileptic doses are pregabalin 150 to 600 mg daily and gabapentin 600 to 1800 mg daily.

Dose reduction is required for reduced renal function.

Efficacy

Gabapentinoids are indicated for treatment of diabetic neuropathy and post-herpetic neuralgia. Typically, only 1 in 8 people obtain a benefit. It is estimated that only 25% of patients with these conditions will experience any benefit from gabapentinoids, and few will experience more than a 50% reduction in pain.

Gabapentin and pregabalin can improve symptoms of restless legs syndrome. They may also be effective for treating chronic pruritus.

Gabapentinoids are unlikely to be of benefit for treating anxiety or non-neuropathic pain, including low back pain, lumbar radicular pain, episodic migraine and sciatica. Only 10% of patients with moderate to severe fibromyalgia experience a 50% reduction in their pain over several months of treatment.

The opioid-sparing effect of gabapentinoids is small and probably not significant.

Regardless of indication, trial dose reduction or deprescribing every 3-6 months to assess ongoing benefits and to reduce the risk of adverse effects. Any beneficial response should be seen after 4 weeks. The aim should be to use gabapentinoids at the lowest effective dose for the shortest time possible.

Side effects

The incidence of adverse effects of gabapentinoids may be increased in older people. Common side effects include dizziness, somnolence (sleepiness), vertigo, and headache. Dizziness or somnolence may increase the risk of falls in older people.

Euphoria is a dose-dependent effect of gabapentinoids, experienced by about 10% of people. Sedation, disinhibition, relaxation and hallucinations can also occur.

Other common psychiatric side effects include confusion, irritability, decreased libido, disorientation and insomnia. These side effects can occur in as many as 1 in 10 people.

Concomitant use of gabapentinoids with opioids and benzodiazepines should be avoided, because of an increased risk of respiratory depression, accidental overdose and death. Concomitant opioid use can also increase the amount of gabapentin absorbed by the body.

Dependence and misuse

Dependence may develop with chronic use of gabapentinoids. Physical dependence (tolerance and withdrawal effects) is slightly less than for benzodiazepines and alcohol. Addiction is less likely than physical dependence.

Pregabalin is more prone to abuse than gabapentin, which may be due to rapid euphoria.

In Australia, one in seven Australians prescribed pregabalin are considered at being at high risk of misuse.

Deprescribing

People prescribed long-term gabapentinoids who experience little benefit or evidence of harms should be deprescribed these medicines.

Gabapentinoids should not be stopped abruptly as withdrawal symptoms may occur, including:

- Anxiety
- Headache
- Insomnia
- Sweating
- Nausea
- Diarrhoea
- Vomiting
- Chills

Agitation, confusion and disorientation occur in about half of people abruptly stopping gabapentin. Tachycardia, hypertension and tremor are also reported. Increased seizures may also occur in people with epilepsy.

As pain and anxiety are withdrawal symptoms from gabapentinoid reduction and discontinuation, the withdrawal syndrome can be mistaken for a return of the condition for which the medicine was prescribed. Withdrawal symptoms can also occur during treatment when doses are omitted or missed. Some people can have ongoing withdrawal symptoms following cessation.

Gabapentinoids should be reduced in dose gradually to avoid withdrawal symptoms. The Australian Medicines Handbook (AMH) recommends gradual reduction over at least a week. Other references suggest reducing pregabalin by 50mg every 1-4 weeks and gabapentin by 300mg every 1-4 weeks. For average doses, tapering could take between 3 and 12 months.

Primary Health Tasmania deprescribing guidelines suggest a tapering schedule over 4-8 weeks is preferable for patients who have been taking gabapentinoids long term (greater than 6 months) or at high doses.

Newer guidance in the *Maudsley Deprescribing Guidelines* recommends making dose reductions by smaller and smaller decrements, down to very small final doses, before final cessation. Deprescribing may take up to 2 years or even longer.

Slow tapering may require halving or quartering of gabapentin tablets. Gabapentin capsules can be opened, and the contents dispersed in 10-20mL of water, orange juice or pureed foods. The contents of the capsule have a very bitter taste.

Pregabalin capsules are available in many strengths, including 25mg, 75mg, 150mg and 300mg capsules. For very small doses, pregabalin capsules can be opened and the contents dispersed in 10-20mL of water, then shaken or stirred, then the dose measured immediately.

Summary

Gabapentinoids are only moderately effective in treating neuropathic pain, specifically postherpetic neuralgia and diabetic neuropathy. They are ineffective for sciatica and for non-neuropathic pain. People at increased risk of harm from gabapentinoid adverse effects (cognitively impaired, renal impairment, gait disorders, co-prescribed other CNS active agents) should have their use of gabapentinoids reviewed frequently with a view to dose minimisation or cessation. Abruptly stopping gabapentinoids may result in withdrawal symptoms. Slow gradual tapering is recommended.

References

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