Clinical Quality and Education

Medicines Update Bulletin

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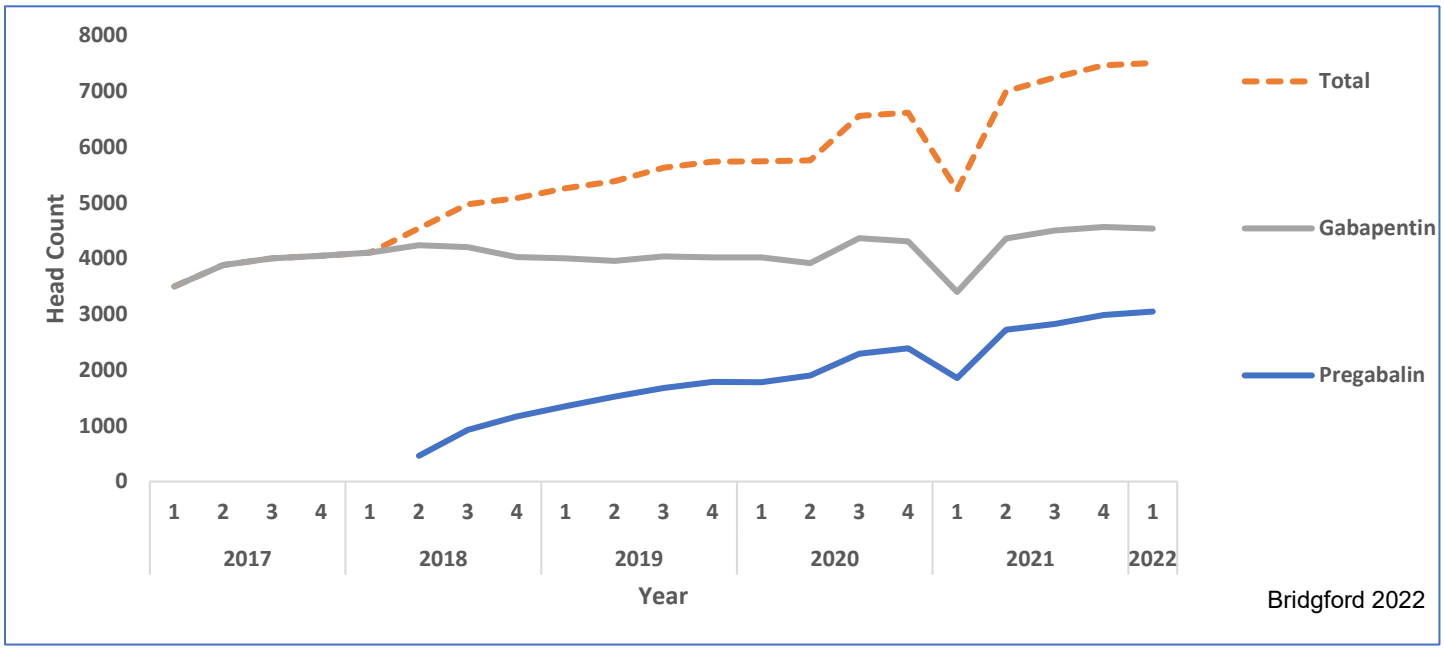
Gabapentinoids

Limited efficacy and growing international safety and abuse concerns

Canterbury Gabapentinoid Dispensing Trends



- Gabapentinoids, such as gabapentin and pregabalin, are only effective in a minority of people and should be deprescribed if no benefit is obtained
- Little evidence for efficacy of either drug for non-neuropathic pain
- Both pregabalin and gabapentin may cause addiction and serious adverse effects, particularly when used in combination with CND depressants such as opioids
- Both drugs have abuse and diversion potential

Clinical Quality and Education Team comment:
Pregabalin and gabapentin may be useful in neuropathic pain, but there is little evidence to support their use for non-neuropathic pain. Adverse effects are common and overseas experience suggests significant risk of misuse, drug-related deaths, suicide, and increased risk of death from trauma. We suggest limiting the use of these drugs to patients with neuropathic pain and as an adjunct for focal seizures. Patients should be fully informed about the risks of treatment and clinicians should be alert to the risk of drug misuse.

Indications

International and national trends reveal a substantial increase in prescribing of gabapentinoids[1-4]. In New Zealand, pregabalin and gabapentin are indicated for neuropathic pain, and focal seizures[5,6]. Both are now fully funded without restriction[7]. Gabapentinoids are also used for many unapproved indications where there is little supporting evidence. This increasing use of gabapentinoids is concerning, given the questions around efficacy and abuse potential outlined below.

Efficacy Questions

While some people with chronic neuropathic pain conditions such as diabetic neuropathy and post herpetic neuralgia can benefit from this therapy (NNT for ≥ 50% pain intensity reduction 7.7 for pregabalin and 6.3 for gabapentin), there is evidence that many with chronic non-neuropathic pain experience little relief[1,2,8]. When used in chronic neuropathic pain, a **minority** of patients will get substantial benefit from gabapentinoids, **more** will get moderate benefit and **many** will get no to minimal benefit, or will stop taking it due to adverse effects[9-11]. Gabapentinoids appear to be no better than tricyclic antidepressants, or each other, for neuropathic pain[7].

Evidence from RCTs does not support the widespread use of pregabalin and gabapentin off-label to manage non-specific chronic low back pain, noting an increased risk of adverse effects and minimal to no evidence of benefits compared to placebo or other analgesics[12]. Further studies on osteoarthritis and sciatica treated with gabapentinoids, found that there was little evidence to support their efficacy[13,14].

Adverse effects

Adverse effects include:
Dizziness/balance (19-31%), sedation (14-29%), dry mouth (15%), weight gain (15 % - > 5kg), peripheral oedema (7%), constipation (6%), euphoria (6%), abnormal thinking (6%)[7].

Slower dose titration may be necessary, particularly in susceptible individuals (e.g. frail elderly) to minimize dose-related adverse effects. Dose reduction is required in renal impairment[15].

International studies highlight evidence that gabapentinoid use can be associated with increased risk for unintentional overdose, suicidal behaviour, road traffic accidents and injuries, with pregabalin use demonstrating a higher incidence than gabapentin[16].

Additionally, gabapentinoids have CNS depressant risks and have been causally linked to drug-related deaths overseas, particularly if opioids are used in combination. Increased prescribing of gabapentinoids has correlated with an increased number of gabapentinoid related deaths[17,18].

Gabapentin and pregabalin should not be used together[7]

Abuse Potential

Gabapentinoids may offer prescribers an alternative to opioids for some types of neuropathic pain[3]. **However, there is a risk that as opioid prescribing decreases, gabapentinoid abuse and diversion may rise**. A UK survey indicated that misused gabapentinoids were most often sourced from a healthcare provider (63.1%), with other sources including family or acquaintances (57.8%), the internet (47.3%) and overseas sources (7.8%)[2].

In April 2019 the UK, reclassified both pregabalin and gabapentin because of risks of dependency and abuse from prescription medicine to a controlled drugs C classification under the 'Misuse of Drug Act 1971'. Class C limits supply to 30 days with no repeats[19]. Lorazepam and tramadol are also included in this category[20].

Gabapentinoids can produce euphoria, alcohol and benzodiazepine-type effects[17]. In recent years there has been a rapid increase in misuse of these drugs[8]. One systematic review reported the biggest risk is for those with a current or past substance abuse history[18,21]. Gabapentinoid abuse has been estimated to occur in 1.6% of the general population (who do not have a history of drug abuse), increasing by 3% to 68% among opioid abusers[22]. In Australia, pregabalin's use has escalated since it became subsidised in 2013. The increased use has been accompanied by an increased number of pregabalin related poisonings and deaths[23]. Pregabalin appears to have the greater misuse potential than gabapentin, possibly due to its rapid absorption and faster onset of action[17,24].

An abuse potential risk assessment should be completed before prescribing gabapentinoids[23]. Equally, caution should be applied when co-prescribing other medications such as benzodiazepines and opioids[7,21,23,25]. Patients need to be fully informed about the risk and benefits of gabapentinoid use[2].

Withdrawal

Pregabalin and gabapentin are both associated with withdrawal symptoms[5,6]. Discontinuation symptoms are dose dependent and varied[17]. It is recommended a gradual dose reduction over seven days when withdrawing treatment. Sudden discontinuation may result in sweating, insomnia, and anxiety[7].

Recommendations

NICE recommends early and regular assessments of patients prescribed all pharmacotherapies for neuropathic pain. While markers for potential misuse may emerge later in treatment, prescribers should always be alert to these even at the start of a treatment episode so that misuse can be avoided[26]. Clinicians and pharmacists need to monitor patients for use of multiple prescribers, mood changes and requests for early repeat prescriptions and rapid dosage increases[3,24].

An analgesia plan using the biopsychosocial model of pain management may be useful; this includes a discussion with the patient and provision of a written document with clear instructions on how to take gabapentinoids. A review schedule should be included[7]. A pre-treatment agreement (available on HealthPathways) may also be appropriate.

The rapid growth in prescribing of pregabalin locally and nationally in the last twelve months without a corresponding drop in gabapentin use, suggests it may be being prescribed for indications which are unlicensed. It is good practice and may become a requirement in the new medicines regulations being drafted, to document that the patient has been informed and agrees to the drug being used off-label and that they understand the potential harms as described.

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