J R Coll Physicians Edinb 2017; 47: 310–3 | doi: 10.4997/JRCPE.2017.402 **PAPER**

Gabapentin and pregabalin: do the benefits outweigh the harms?

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Abstract

Gabapentin and pregabalin prescribing in Scotland has increased substantially over recent years. Evidence suggests that prescribers may be advocating the use of these medicines off-label to avoid prescribing opioid analgesics. The evidence to support gabapentin and pregabalin use in non-neuropathic pain disorders indicates they are less effective than several other licensed non-opioid analgesics. Notably, patients may not benefit from gabapentin and pregabalin but remain at risk of adverse drug reactions. Furthermore, greater availability has resulted in increased diversion of gabapentin and pregabalin; creating problems within the opioid misuse population and prison service. As a consequence, both gabapentin and pregabalin may soon be controlled under the Misuse of Drugs Act 1971. Prescribers should be aware of the very limited clinical evidence for use of gabapentin and pregabalin outside their licensed indications, as well as their capacity to do harm.

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Introduction

In the USA, harms associated with opioid dependence have paralleled the increasing prescription of strong opioids.[1] From 1999 to 2015, more than 183,000 deaths have been attributed to prescription opioids, and opioid abuse is a major cause of disability.[2,3] Over this period, increased opioid prescribing and drug-related deaths have also been seen in the UK.[4,5] As prescribers and the public become increasingly aware of the potential risk of opioid dependence, the pharmacological management of chronic pain has never been under greater scrutiny. Chronic pain affects between a third and a half of the UK population and the moral imperative to treat pain has likely provoked the rise in opioid use.[6,7] UK guidelines for the management of chronic lower back pain recommend a step-wise approach to pharmacological management, and weak opioids are only considered if a NSAID is contraindicated or has been ineffective.[8] Unfortunately, however, many non-opioid analgesics have limited utility in clinical practice (for example, NSAIDs are a common cause of adverse drug reactions resulting in hospitalisation).[9]

It is understandable that prescribers would attempt using a non-NSAID, non-opioid analgesic in response to the twin pressures of an opioid epidemic and the burden of chronic pain. Changing prescribing practice in Scotland has resulted in a proportional increase in the prescription of strong opioids, but also growing use of the non-opioid analgesics gabapentin and pregabalin.[10] In the UK, gabapentin and pregabalin prescribing has increased by 350% and 150% over 5 years, respectively.[11] This trend is likely due to avoidance of opioid analgesics,[12] despite the use of gabapentin and pregabalin for non-neuropathic pain being unlicensed and ineffective. Patients inappropriately prescribed gabapentin or pregabalin may not benefit and may be exposed to potential harms, which broadly fall into two categories. First, by causing an adverse drug reaction or toxicity, e.g. central nervous system effects (headache, visual disturbance, drowsiness, agitation, delirium, lethargy); cardiac effects (tachycardia, bradycardia); disturbances in muscle control and movement, and gastrointestinal symptoms. Second, gabapentin or pregabalin prescription may result in drug misuse or diversion (the transfer of any legally prescribed substance from the individual for whom it was prescribed to another person for illicit use).

History of gabapentin and pregabalin

Gabapentinoids are close analogues of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Our review is restricted to gabapentin and pregabalin, which are effective in the treatment of neuropathic pain.[13] Their mechanism of action appears to be unrelated to direct effects on the GABAergic system, and their beneficial effect is exerted through modification of the alpha2-subunit of voltage gated calcium channels.[14]

Gabapentin was first licensed as an adjunct antiepileptic therapy in 1993, later gaining licensing approval for treatment

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of post-herpetic neuralgia. Despite this limited indication, off-label prescribing of gabapentin for other pain syndromes increased in the 1990s, a phenomenon largely attributable to extensive marketing campaigns in the USA, and assumed safety.[15,16] Ultimately, Pfizer subsidiary Warner-Lambert admitted to violation of US Federal regulations by promoting the drug for pain, psychiatric and other unapproved conditions. Pregabalin was approved for treating diabetic neuropathy and post-herpetic neuralgia in 2004 and is now available as a generic medication.

What are the indications for gabapentinoids?

In the UK, gabapentinoids are currently licensed for the treatment of focal seizures and peripheral neuropathic pain. Pregabalin is also indicated for use in central neuropathic pain and generalised anxiety disorder. The increased use of these drugs cannot be fully explained by increasing prevalence of their licensed indications. A UK study in primary care noted that almost two-thirds of pregabalin prescriptions did not have a diagnostic code corresponding to an approved indication.[17] Healthcare professionals should be aware of their greater responsibilities when prescribing off-label medicines, in comparison to a licensed drug.[18] Prescribers must be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative, including confidence in the balance between the potential benefit and the risk of harms.

What is the current evidence for the use of gabapentinoids in pain management?

Gabapentinoids are considered to be effective for neuropathic pain. Consequently, both gabapentin and pregabalin are recommended by the National Institute for Health and Care Excellence for this indication.[19] Cochrane reviews provide a similar conclusion with regard to their efficacy, noting 3 or 4 out of 10 participants achieved a greater than 50% reduction in neuropathic pain with gabapentin, compared with 1 or 2 out of 10 for placebo.[20] Prescribers should be aware that over half of those treated with gabapentin do not have worthwhile pain relief but may instead experience adverse effects. Similar issues affect pregabalin, a treatment which will substantially benefit only a minority of patients with neuropathic pain.[21] Prescribers should also be aware of the evidence base from which this advice is derived; direct evidence of benefit only exists in diabetic neuropathy and herpetic neuralgia. Extrapolation of presumed benefit from this narrow subset of patients may not accurately reflect 'real world' benefit for other causes of neuropathic pain.

A wide range of off-label, non-neuropathic pain uses have been proposed for gabapentinoids but these come with a limited evidence base that is underpowered and/or from studies open to bias.[8,22] Notably, in the majority of reports promoting the benefits of off-label use, gabapentin is not the optimal treatment.[23] Existing evidence for the use of gabapentinoids in chronic lower back pain demonstrates the risk of adverse effects without any clear benefit.[24] Surprisingly, there is inconsistent evidence of benefit even if chronic back pain is related to radiculopathy.[25] Pregabalin is licensed for the management of fibromyalgia in the USA but not in the UK. Pregabalin produces a major reduction in pain intensity events for a small proportion of people (about 10% more than placebo), similar to other licensed medicines in fibromyalgia (milnacipran, duloxetine).[26] There is insufficient evidence to support the use of gabapentin in fibromyalgia.[27] In other chronic pain syndromes, e.g. chronic pain due to chronic pancreatitis, short-term use of pregabalin may decrease short-term opioid use and short-term pain scores, but increases rates of adverse events compared to placebo.[28]

Efficacy of gabapentinoids in acute pain management has also been investigated, yet opinions remain divided about their clinical effectiveness. Superficially positive trials supporting the use of gabapentin in postoperative pain reveal a high number-needed-to treat, suggesting limited clinical utility and poor performance in comparison to alternative analgesics, i.e. NSAIDs and paracetamol.[29] Interestingly, postoperative gabapentinoid use may reduce total morphine consumption and morphine-related complications (nausea and itch) at the risk of increased sedation and visual disturbance.[30,31] There is no evidence to suggest gabapentinoids reduce the risk of postoperative chronic pain.[32]

Patterns of misuse

Gabapentin was originally considered to have no misuse potential, an assumed attribute that likely contributed to high rates of off-label prescribing.[16] While meaningful modulation of the dopaminergic reward pathway is yet to be proven, GABA inhibits the release of excitatory neurotransmitters, explaining the anxiolytic and sleep-modifying activities of gabapentinoids.[33] Reports of harm related to gabapentinoids are currently few, in comparison to opioids, yet the increasing trend in mortality is concerning in the face of their increasing availability. Between 2013 and 2015 in the UK, deaths reported to involve gabapentinoids increased by almost 400%, from 36 to 137.[34,35]

Misuse is defined as use of a substance for a purpose not consistent with legal or medical guidelines, such as taking another person's medication or taking a higher dosage than prescribed.[36] Current estimates suggest 1% of the general population misuse gabapentin, as do 15–22% of people who misuse opioids, and 40–65% of people with gabapentinoid prescriptions.[37] Reports of misuse normalised to prescription number would suggest that drug dependence issues are more frequently reported with pregabalin than gabapentin[22] and cases of pregabalin misuse are increasing.[38] Pregabalin may have a higher misuse potential than gabapentin due to its rapid absorption and faster onset of action.[39]

The issues underpinning misuse of gabapentinoids are not yet fully understood. Unsurprisingly, known substance misuse is associated with misuse of pregabalin.[22,40,41] Opioid users report that pregabalin reinforces the effects of opioids and reduces the undesirable effects of withdrawal symptoms,

making it widely sought after for misuse.[35,42] Opioid treatment programmes have reported approximately 10% of patients test positive for pregabalin, the majority of whom were not prescribed this medication.[43,44] Co-misuse of gabapentinoids and opioids is particularly concerning because high-dose pregabalin may exaggerate the respiratory depression seen with opioid use.[35] Seventy-nine percent of deaths attributed to gabapentinoids also involved opioids. This statistic may reflect causation due to worsened respiratory depression or an association made at post-mortem due to the increasing co-misuse with opioids.[35]

The misuse of gabapentinoids is well described in the prison population. In February 2015, UK prisons reported high numbers of prisoners being prescribed gabapentinoids in a manner not in keeping with best clinical practice.[34] Due to the high potential for diversion, some prisons refuse to prescribe pregabalin. This leads to inequality between care in prison and the community, and resulted in prisoners reporting inadequate pain management.[45]

As we become increasingly aware of the potential harm associated with gabapentinoids, several countries have acted in an attempt to reduce harm from diversion. Pregabalin is placed under Schedule 5 of the US Controlled Substances Act and was listed as a new recreational psychoactive substance by the relevant EU agencies in 2010.[42] In January 2016, the UK Advisory Council for the Misuse of Drugs recommended that both pregabalin and gabapentin should be controlled under the Misuse of Drugs Act 1971 as Class C substances and scheduled under the Misuse of Drug Regulations 2001 as Schedule 3 (actions that will not preclude legitimate use on prescription).[34] This recommendation has been accepted in principle by the Minister for Vulnerability, Safeguarding and Countering Extremism, pending public consultation.[46]

Conclusion

Ongoing use of gabapentinoids in the management of chronic pain is driven primarily by the imperative to treat this disabling condition, with a lack of good alternatives and the perception these drugs are safe. Emerging evidence of lack of effectiveness appears to have had little impact on prescribing practice.[16] Within chronic pain management, patient and prescriber expectation is high; advocating maximum possible pain relief for every patient in pain.[47] What opioids and gabapentinoids have in common is their anxiolytic and dissociative effects, addressing comorbid issues often associated with chronic pain.[48–50] Improvements in a patient's quality of life may not be mediated entirely through pain relief but linked to pregabalin's effects on sleep disturbance and anxiety.[51] Consequently, judging the effectiveness of gabapentinoids for pain control may be difficult as they may have positive consequences on a comorbid anxiolytic element. While addressing psychological factors is important in chronic pain, gabapentinoids are not the best approach.[52]

The burden caused by harm and diversion of gabapentinoids is increasingly under scrutiny. We must be confident our prescribing decisions will be to the overall benefit of our patients. Similar to the ongoing opioid crisis, we as prescribers must be conscious of the potential to do harm, both to our patients and society as a whole.

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