Guide to the management of gabapentinoid misuse

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In light of the government’s proposals to reclassify pregabalin and gabapentin as Class C controlled drugs due to the risk of misuse, this article examines the extent of the problem of gabapentinoid misuse and its effects, and provides practical advice to prescribers on reducing these harms.

Pregabalin was launched in the UK in 2004 while gabapentin was first authorised in the UK in 1997. Both drugs were originally licensed for seizure disorders but now have multiple licensed indications. In England during 2016, over 12 million prescription items were dispensed for gabapentinoids as a group. The Advisory Council on the Misuse of Drugs (ACMD) reported that pregabalin prescribing in the UK increased by 350% in the five years to 2012 while gabapentin prescribing increased by 150% during the same period.

There has been growing concern about the misuse potential of the gabapentinoids as a group and in particular pregabalin, as reported in the 2016 ACMD review of this class of drugs. This concern led to the government launching a consultation on the reclassification of pregabalin and gabapentin as Class C controlled drugs under the Misuse of Drugs Act, which ended on 22 January 2018.

This article discusses both drugs but with a particular emphasis on pregabalin, which presents with a greater misuse potential than gabapentin. It explores the current (licensed and unlicensed) indications and the pharmacology of the two drugs, aspects of their misuse potential and effects of this misuse on the individual. Finally, it provides advice for prescribers on managing the misuse of gabapentinoids and supporting patients who are discontinuing a gabapentinoid.

Licensed uses

The gabapentinoids have a wide range of licensed uses. Pregabalin and gabapentin are both licensed for neuropathic pain and epilepsy. Pregabalin also has a licence for the treatment of generalised anxiety disorder (GAD). Pregabalin is recommended by NICE as a second-line pharmacotherapy for GAD if a patient cannot tolerate SSRIs or SNRIs. NICE recommends offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia). Off-label uses for gabapentinoids include...
the treatment of migraine, alcohol use disorders, mania and bipolar disorder.⁷

NICE recommends early and regular assessments of patients prescribed pharmacotherapies for neuropathic pain, including the gabapentinoids. The assessment should include dosage titration, tolerability and adverse effects.⁶ While markers for potential misuse (see Table 1) 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.

Pharmacology
Both gabapentin and pregabalin are structurally similar to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and rapidly cross the blood-brain barrier. The gabapentinoids bind to the alpha-2-delta subunit of the voltage-dependent calcium channels in the CNS resulting in a decrease in the excitatory neurotransmitters glutamate, noradrenaline, substance P and calcitonin gene-related peptide. Both drugs produce pharmacological effects that are similar in nature to those produced by the inhibitory neurotransmitter GABA, ie they exhibit GABA-mimetic properties.

Pregabalin is rapidly absorbed on an empty stomach with peak plasma concentrations occurring within one hour. It has a high bioavailability (≥90%) and a mean elimination half-life of 6.3 hours and undergoes almost no metabolism with the parent drug being largely excreted unchanged in the urine. The linear pharmacokinetics of pregabalin (compared with the non-linear pharmacokinetics of gabapentin) allows straightforward dosing regimens and a predictable response. Pregabalin also has a higher binding efficiency than gabapentin and higher potency (2.5 times greater than gabapentin). The higher potency, quicker absorption and greater availability of pregabalin vs gabapentin makes pregabalin more attractive as a drug of misuse.

The absorption of gabapentin following oral administration is less rapid than pregabalin. Peak plasma concentrations are observed within two to three hours with oral bioavailability decreasing with increasing dose. Absolute bioavailability is reported as 60% for a 300mg capsule.⁴ Gabapentin is also eliminated unchanged through renal excretion with an elimination half-life of between five to seven hours.⁴

Why are gabapentinoids misused?
Gabapentinoids have been reported to produce alcohol/gamma hydroxybutyrate (GHB)/benzodiazepine-type effects mixed with euphoria. Rates of euphoria have been reported at between 1 and 12% but this has been for therapeutic doses.⁸ Other reported actions include dissociative effects, improved sociability, relaxation and sense of calm, and psychedelic effects. Schifano et al. reported that significant psychotropic effects are associated with higher doses and “idiosyncratic (ie IV, rectal, intranasal) drug intake modalities” but the most common route of misuse remains oral.⁸

Polydrug misuse remains a significant concern with the cohort of service users that may misuse gabapentinoids and has been implicated in the recent rise in drug-related deaths for the gabapentinoids. A recent review in the journal *Addiction* suggests that pregabalin is used to enhance the effects of heroin but for some people it may also be used to help support the reduction in use of heroin.⁷ This synergistic effect can also be used to reduce the amount of heroin needed to provide a similar psychoactive effect. Mixed misuse with antipsychotic drugs can also be a problem – as demonstrated in a case report describing the misuse of gabapentin and quetiapine.⁵ Pregabalin and gabapentin have also been used to enhance the effects of alcohol and other prescribed and non-prescribed drugs including methadone.⁷,⁸,¹⁰ Animal models also support the hypothesis that the effects of morphine and pregabalin are potentiated when taken together.

The onset of action of the gabapentinoids ranges from between 10 minutes, ie quick acting, and two hours depending on the route of administration and both dependent and recreational use has been reported. Rapid development and extinction of tolerance to the effects of gabapentinoids has also been documented.¹¹

The effects associated with pregabalin at increasing doses, as reported by users, is summarised in Box 1.

Evidence for and prevalence of gabapentinoid misuse
There is now a rich source of anecdotal reports that support significant misuse of gabapentinoids both in the UK and internationally, such as the user reports on the Erowid website.¹² Following the introduction of pregabalin to the UK in 2004, the Medicines and Healthcare products Regulatory Agency (MHRA) received its
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According to pregabalin (mis)users, different doses are associated with a vast range of effects:

- **600mg**: stumbling, disorientation, increased physical and psychological awareness, difficulty driving, slurred and broken speech, hearing and visual alterations/hallucinations, double and blurred vision, uninhibited behaviours, talkativeness, increased body energy, increased sexual performance
- **900mg**: strong feelings of drunkenness, difficulty walking, alteration of colour perception, little euphoria
- **1200mg**: drowsiness, euphoria, entactogenic (empathetic) feelings, ie similar to Ecstasy
- **>1500mg (to 5g)**: uncontrollable drowsiness, frequent hallucinations, great euphoria, frequent dissociative events (described as dextromethorphan/DXM-like dissociative effects), behavioural inhibition, anxiety, and necessity to move

**Box 1.** Online user accounts of pregabalin effects, according to dose

First report of withdrawal symptoms in 2005. Following this, the first report of drug use disorder was reported in 2006 and drug dependence in 2009. Evidence from UK secure settings suggests significant use of gabapentinoids. Prescribing of gabapentin and pregabalin occurs in 2.8% of the prison population, which is twice the rate found in the general population. Category A prisons having the highest rates and 47% of prisoners in this cohort are also prescribed opioid substitution treatments (OST). The ACMD has also noted that the prescribing of the gabapentinoids in secure environments often does not meet “best practice guidelines”. The Pain Management Formulary for Prisons classifies the gabapentinoids as drugs for “limited use” and aims to challenge current practice and introduce a framework around the management of pain in secure settings.

The DrugScope 2014 street survey highlighted the problem of misuse quoting “significant use... chiefly among Britain’s opiate-using and prison population”. The effects of gabapentinoids are described within the report as “horrendous and life threatening” with one drug worker reporting the prevalence of use in one homeless hostel at 70% of residents. The manufacturers of both drugs have also warned prescribers of the risk of abuse and dependence, highlighting the need for a careful evaluation of patients with a history of drug or substance abuse. International reports from Finland, Germany and the USA suggest a global problem with gabapentinoid misuse. In Finland, a study of toxicity reports of drug-related deaths between 2010 and 2011 suggest a “substantial increase” in drug-related deaths involving pregabalin and opioids, with opioids present in 90% of deaths involving gabapentinoids. The study also reported a seven times greater incidence of pregabalin misuse in drug-related deaths compared with gabapentin. In Germany, pregabalin misuse has been reported to the German medical regulatory body with an increasing frequency since 2008, while the USA placed pregabalin under the Controlled Substances Act in 2005, citing that misuse may lead to “limited physical dependence or psychological dependence”.

The prevalence of gabapentinoid misuse has been assessed in two systematic reviews. An international systematic review of 59 studies indicates a gabapentinoid abuse prevalence of 1.6% in the general population. This prevalence increased to 3–68% among opioid abusers. Risk factors for misuse were identified as a history of substance abuse (particularly opioids) and psychiatric co-morbidities. Another systematic review looking at gabapentin only reported a 1.1% prevalence of gabapentin misuse in the general population, which increased to 15–22% within “opioid abuse samples”.

Drug-related deaths and gabapentinoid misuse

The CNS depressant effects of the gabapentinoids and opioids (drowsiness, respiratory depression and respiratory failure) are a significant risk and have been implicated in drug-related deaths. Deaths where gabapentinoids were mentioned on death certificates in England and Wales have increased from less than one a year before 2009 to 137 deaths in 2015. In 79% of these deaths, opioids were also mentioned. This increase in drug-related deaths was also shown to correlate highly with prescribing data, ie increased prescribing of gabapentinoids (see Figure 1).

In summary, we have the “perfect storm” of the summation of CNS effects through polydrug misuse, an increase in prescription numbers, and drug effects that cannot be reversed with an antidote (although naloxone will support the reversal of the opioid element of a drug overdose), which all contribute to the risk of drug-related death.

How can patients be supported to discontinue gabapentinoids safely?

Although there is insufficient evidence to support practitioners in helping patients discontinue gabapentinoids, there are some practical guidelines that provide a framework for the development of an appropriate recovery plan. Harm reduction also remains an important component of the advice practitioners should provide to patients.

Discontinuation symptoms of gabapentinoids are varied and will be dependent on the dose consumed and the route of administration. Table 2 summarises these symptoms for both gabapentin and pregabalin for patients reducing from therapeutic doses, as outlined in the summaries of product characteristics. The manufacturer of pregabalin has noted that the severity of symptoms and their incidence “may be dose-related” and prescribers should take this into account when managing a pharmacological withdrawal episode.
A more varied presentation of withdrawal symptoms has been reported in the medical literature for both gabapentin and pregabalin. A review of gabapentin misuse case studies by Mersfelder et al. reported withdrawal symptoms beginning between 12 hours and seven days after cessation of use with the majority of cases occurring between 24 and 48 hours. Agitation was reported in more than half of the cases with confusion and disorientation reported in 45% of cases. Other common symptoms included diaphoresis (36%), non-specified GI symptoms (23%), tremor, tachycardia, hypertension (each 18%) and insomnia (14%). Individual cases also presented with akathisia, catatonia and seizures. Where gabapentin was reintroduced the withdrawal symptoms resolved.

A case study from Grosshans et al. presents the withdrawal symptomology associated with pregabalin at supra-therapeutic doses. The authors report the case of a 47-year-old male consuming the equivalent of 7500mg pregabalin daily. On reduction, the patient experienced sweating, unrest, arterial hypertension, tremor and craving for pregabalin.

Both service users describe their withdrawals from therapeutic doses of pregabalin (450mg and 600mg respectively) as “hellish”. Considering the link between dose and symptoms suggested by the manufacturers, a collaborative and more conservative approach seems a pragmatic response. Patients on supratherapeutic doses of gabapentinoids should have a reduction plan discussed that allows for an illicit reduction in the community. If the prescriber decides to prescribe above the maximum dose in the summary of product characteristics, this should be for a short period of time with an aim to reduce the patient to below the licensed maximum dose within the guidance provided by PHE. The maximum reduction rates suggested for the gabapentinoids within the PHE guidelines are:

- 50mg to 100mg a week for pregabalin and
- 300mg every four days for gabapentin.

There is insufficient evidence to suggest what adjuvant medication could be used to support patients, so no recommendations can made. Nevertheless, a reduction in the pharmacological agent used to manage the primary indication should necessitate a review. For example, the treatment of GAD may necessitate a transition to an SSRI. This should also include a review of the psychosocial interventions both to support the patient in managing the withdrawal from the gabapentinoid and to support the patient in managing the presentation of the primary indication. This may include, for example, engagement with cognitive behavioural therapy.
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<td>Flu syndrome, pain and hyperhidrosis</td>
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Table 2. Discontinuation symptoms for pregabalin and gabapentin withdrawal, as outlined in the summaries of product characteristics

therapy services for supporting patients in the management of their GAD.

Practical advice for prescribers
To prevent the emergence of problems and to support patients in reducing harm associated with the misuse of gabapentinoids, some practical steps can be employed. These practical advice tips have been brought together from a variety of sources. An excellent document supported by the Northern Ireland Public Health Agency – Pregabalin: Guidance for People Working with Pregabalin Users – is available, which provides more comprehensive advice, especially around harm reduction, for patients misusing pregabalin.

- Ensure a robust assessment process is undertaken and careful consideration is given before prescribing gabapentinoids to patients with a history of substance misuse or those who have recently been released from prison. Use an alternative medication when clinically appropriate.
- When gabapentinoids are prescribed, warn patients about the benefits and risks (including dependence) of the medications.
- Review treatment regularly to ensure efficacious prescribing and monitor for potential misuse markers (see Table 1).
- Ensure prescribed doses do not exceed the therapeutic dose ranges (doses will also need to be adjusted in patients with reduced renal function).
- If there is a clinical need to prescribe a gabapentinoid to a service user with a history of drug or alcohol misuse, ensure that it is prescribed as regular short courses, eg every seven days, rather than the standard 28-day prescription to improve monitoring for overuse and to minimise the risk of binge use.
- If a gabapentinoid is used for neuropathic pain, review at eight weeks following initiation and discontinue (gradually) if ineffective.
- Misure of any psychoactive medication is often linked to either a mental health co-morbidity and/or inadequate management of the primary physical health presentation. Ensure this is reviewed and managed appropriately especially if the gabapentinoid is removed from the pharmacotherapies available.
- Harm reduction advice for illicit users should include advice to take the medication orally and avoid injecting, and to follow the adage of “start low and go slow”. The dangers of polydrug use, including the increased risk of drug-related death, should also be discussed.
- Ensure naloxone (Prenoxad injection) is issued to service users who also use opioids (and provide advice on its use as well as basic harm reduction advice). Many drug and alcohol specialist providers now supply this routinely to service users who misuse opioids – contact your local provider for more details.
- When supporting service users with a planned reduction in gabapentinoid use, use the schedules recommended by PHE to plan a collaborative process.
- Be aware of services such as the Battle Against Tranquilisers (BAT), who provide support for service users with pregabalin use disorders in the Bristol area, as well as nationally through their website and national support helpline. UK SMART Recovery also provides support for individuals who want to seek abstinence from drug misuse through a network of self-help and mutual aid meetings. If you need support, please speak to your local specialist drug and alcohol provider who can also give practical support and advice on the management of this service user group.
- Improve your knowledge as a prescriber to ensure you can provide appropriate advice and treatment when needed. This article and the associated references should help to support your learning.

Summary
Pregabalin and gabapentin remain important evidence-based treatments for a number of conditions. However, emerging evidence suggests that prescribers should adopt a cautious approach to the assessment and management of patients who are prescribed gabapentinoids. Both misuse and dependence have been reported with gabapentinoids, and they have been widely implicated in a number of drug-related deaths.

Prescribers should make a balanced judgement on prescribing gabapentinoids based on a robust assessment process, especially when prescribing to patients who may be at risk of misusing the medications. Patients should be provided with information about the benefits and risks of taking gabapentinoids and should be supported if they want to undertake a detoxification programme. Harm reduction interventions remain an important approach to this complex phenomenon.

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Declaration of interests

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