**ABSTRACT**

**AIMS:** Pregabalin has not been used widely in New Zealand to this point as it has not been funded, but from May 2018 it will be available fully subsidised. This paper intends to highlight the issue of pregabalin misuse, a concern that will be unfamiliar to most clinicians in New Zealand.

**METHODS:** A review of the literature of papers documenting the misuse of gabapentin and pregabalin was conducted with a specific focus on pregabalin.

**RESULTS:** There is a growing body of evidence regarding the potential of misuse of pregabalin. It produces a range of sensations, including euphoria, sedation and dissociation. It is commonly used in conjunction with other drugs, most notably sedatives and opioids, which leads to an additive effect. Although generally safe when taken alone, pregabalin is a growing feature of drug-related deaths.

**CONCLUSIONS:** Prescribers need to be alert to the potential of pregabalin misuse. This should be achieved through prescribing with great care (not prescribing to new or unknown patients; not in response to direct patient requests for it by name; supplying in limited quantities), regular review of patients and stopping treatment, by slow withdrawal, when lack of efficacy is seen.

In October last year, PHARMAC opened a consultation on the funding of pregabalin in New Zealand. Up until now, pregabalin has not been subsidised for use in New Zealand. Now, from 1 May 2018, pregabalin will be available fully subsidised with no restrictions on prescribing.

Throughout history, the medical profession has played a significant role in the misuse and dependence on drugs, including the barbiturates, the benzodiazepines and more recently, oxycodone.

This paper intends to highlight the issue of pregabalin misuse, a concern that will be unfamiliar to most clinicians in New Zealand.

**Pregabalin**

Pregabalin is a drug of the gabapentinoid class, a group that also includes gabapentin, a drug most New Zealand prescribers will be familiar with.

Pregabalin, (S)-(+)3-isobutylgaba (marketed under the brand name Lyrica®) is a gamma-butyric acid analogue that has a novel mechanism of action shared only by gabapentin. Despite the close resemblance of these drugs to gamma-amino butyric acid (GABA), their pharmacological action is unrelated and, although the precise mechanism of action is unclear, is understood to occur through binding to calcium channels in the central nervous system.

Gabapentin (Neurontin®) was initially developed as an antiepileptic drug in the mid-1980s before its action as an ‘antihypalgesic’ agent was identified. In Europe, pregabalin was initially authorised for the treatment of peripheral neuropathic pain and epilepsy in 2004 with extensions to add generalised anxiety disorder in January 2006, and central neuropathic pain in July 2006.

In New Zealand, the NZ Formulary (NZF) and data sheet currently list pregabalin as indicated for neuropathic pain and adjunctive therapy for focal seizures with or without secondary generalisation. The NZF also lists it for generalised anxiety disorder, although this is an unapproved indication.
Pregabalin is more rapidly absorbed than gabapentin, and it has a higher bioavailability. The maximum plasma level of pregabalin is reached within one hour of taking a dose; gabapentin takes 3–4 hours to reach maximum plasma concentration. Pregabalin may have a higher addiction potential than gabapentin due to its rapid absorption and faster onset of action.

The history of pregabalin licensing and the first discussions of misuse

Pregabalin was introduced in 2004. Prior to this, pregabalin had not been available in any form, so no experience of its use existed.

When pregabalin was approved for use in the US on 31 December 2004, the Food and Drug Administration (FDA) recommended the drug was controlled in Schedule V of the Controlled Substances Act. A key paper in this decision making was the Abuse Liability Study ‘098’. Using this, the FDA determined that the drug was liable to misuse. The FDA pointed out that 3.7% of patients taking pregabalin during studies experienced euphoria, compared to only 0.5% of patients who were administered a placebo. This euphoria continues for a ‘considerable time’ after initiation of treatment (median duration seven days) but diminishes on continued use. The same report stated that the FDA considers euphoria to be an uncommon adverse event for approved drug treatments.

In addition, withdrawal of pregabalin was noted to result in a discontinuation syndrome, however this was considered to be reported at rates lower than for a drug with a ‘classic discontinuation syndrome’. The Abuse Liability Study concluded that a low dose of pregabalin (200mg) was similar in profile to a 15mg dose of diazepam, that is, patients identified it as a sedative. A 450mg dose of pregabalin was more ‘stimulant-like’ than a control of high-dose diazepam, but it resembled diazepam in what the author termed ‘drug-taking behaviour’ with comments including “Good drug effect” and “High”. In contrast, the pregabalin licensing application to the European Medicines Agency (EMA) in 2005 considered misuse as a special safety issue, but dismissed it stating:

“Abuse potential: The abuse potential of pregabalin was studied in a separate study (098) versus diazepam and placebo.

Pregabalin did not have the profile of a prototypic drug of abuse when compared with diazepam.”

Post-launch gabapentinoid misuse

Misuse of gabapentin was documented prior to the approval of pregabalin and recreational misuse of pregabalin was predictable. In the last five years, pregabalin misuse has become established with growing reports in the literature, and more recently in the general press in countries such as the UK.

A paper by Schifano et al in 2011 was the first to raise the misuse of pregabalin. As this paper documents, awareness of the recreational potential of pregabalin and gabapentin was already abundant on websites, internet forums and YouTube. One of the key papers first highlighting misuse to the medical community was the written by Des Spence in the British Medical Journal in November 2013. Since these early papers, the evidence of misuse has grown in a large number of reports, including systematic reviews and also in popular press reports.

Effects

The effects that pregabalin produces when misused can be considered in two ways. Firstly, the drug may be taken to experience the effects induced by the drug itself. Secondly, it may be taken in combination with other drugs, particularly sedatives and opioids, to produce a synergistic effect. When taken, particularly at high dose, the effects are described as a mixture of sedative, psychedelic, dissociative and euphoric.

Deaths

Gabapentin and pregabalin safety has been extensively studied both prior to launch and continues to be monitored. The safety of pregabalin in overdose has been shown in overdoses, with doses of up to 15 grams producing no unexpected adverse effects. The concurrent use of CNS depressants is a well-known risk. The data sheet acknowledges an additive effect with alcohol, benzodiazepines and opioids, and these are drugs that are typically used alongside pregabalin in a polydrug use scenario. Baird et al describe the use of pregabalin to potentiate the effects of methadone, and a recent paper outlines the risk to heroin users from concurrent gabapentinoid misuse.
In the New Zealand data sheet, Pfizer state that there have been recent ('post-marketing') reports of respiratory failure and coma in patients taking pregabalin with other CNS depressant medications.

In the UK, concern has grown over the number of deaths where pregabalin was mentioned on the death certificate. Table 1 shows data from the Office for National Statistics with clear increases in both pregabalin and gabapentin.

Table 1: Number of drug-related deaths where pregabalin and gabapentin were mentioned on the death certificate, deaths registered in England and Wales 2012–2016 (from UK Office for National Statistics).

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<tbody>
<tr>
<td>Pregabalin</td>
<td>4</td>
<td>33</td>
<td>38</td>
<td>90</td>
<td>111</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>8</td>
<td>9</td>
<td>26</td>
<td>49</td>
<td>59</td>
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Concerns surrounding the role of gabapentinoids in opioid overdose deaths were first raised in 2013. In a recent work, Elliott et al describe a series of cases of deaths involving pregabalin and in every case, pregabalin had been consumed alongside other drugs, either prescribed and/or illicit, as well as alcohol in some of the cases. The presence of other drugs is expected given the reported safety of pregabalin alone and most importantly it demonstrates that pregabalin is frequently taken as part of a poly-drug cocktail. Similar toxicological examinations conducted earlier by Häkkinen et al found no fatalities from pregabalin or gabapentin alone.

In 2016, the increase in deaths in the UK linked to the gabapentinoids prompted the ACMD (Advisory Council on the Misuse of Drugs) to recommend they be controlled under UK law. Control of pregabalin in the UK would bring it into line with other jurisdictions including the US. At the current time, pregabalin is classed as a prescription medicine in New Zealand, and not as a controlled drug.

How to approach prescribing

When prescribing pregabalin, practitioners are suggested to use the same cautions that are applied to any drug of misuse, such as opioids or benzodiazepines.

The decision to initiate treatment using pregabalin should only be taken with the considerations typical to any drug, namely suitability for the condition and the evidence for efficacy. Treatment guidelines should be adhered to and other agents tried prior to trialing pregabalin, if appropriate.

Prescribers should exercise caution in the use of pregabalin in any patients with a history of alcohol or drug misuse. The New Zealand data sheet specifies patients should be carefully evaluated for a history of substance abuse and observed for signs of pregabalin misuse or abuse (eg, development of tolerance, increase in dose, drug-seeking behaviour) during treatment.

Prescribers should be aware of patients who increase their dose as this has been linked to patients at high risk of addiction. Prescribers should ensure that patients prescribed pregabalin take it as prescribed and be alert to potential binge use of large doses for pleasure.

Patients who specifically request pregabalin, particularly new or unknown patients, should be treated with extreme caution. Furthermore, it must be remembered that those seeking drugs may not be taking the drug themselves but supplying others on the illicit market—this is especially true for New Zealand, where many drugs are diverted pharmaceuticals due to the limited importation of other drugs.

It is important that pregabalin (and gabapentin) are not simply used to avoid the use of opioids, particularly in patients of concern in respect of potential, or documented, opioid misuse. These drugs may themselves become misused.

Interactions with other sedative medicines as discussed above mean that prescribers need to take additional care when choosing to prescribe this drug. Potential prescribers are reminded of the similar situation with respect to benzodiazepines, which when used alone are generally safe, but when taken in combination with other sedative drugs can potentiate CNS depression.

Review, review, review: Most importantly, any treatment with pregabalin should be subject to regular review. In the treatment of neuropathic pain in particular, the efficacy should be assessed on a regular basis, particularly early on into treatment. Cautious
up-titration of dosage is recommended, but the possibility of treatment failure should be considered if there is a lack of benefit after two to four weeks. Pain relief should be seen in the first few days of treatment with an effective dose, it is not an effect that takes time to develop.26,27 Furthermore, a Cochrane systematic review suggests that 18–28% of patients will need to stop treatment due to adverse events.28

The decision to stop pregabalin treatment should be made carefully (including specialist input then used for seizure disorder) as abrupt cessation can lead to a discontinuation syndrome. Effects seen are predictable and the opposite in action to those of the drug; each of the following has been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness.29 Seizures have also been reported. The severity of withdrawal effects will be related to the dose and the time the drug has been taken.

Pregabalin should be gradually tapered down to minimise these. The taper should extend for a minimum of one week.6,30 Pregabalin is not an opioid drug, however existing guidance, particularly that pertaining to opioids, can be of relevance to its use. Readers are referred to the 2005 paper by Gourlay et al.,31 which discusses many of the salient points in chronic pain prescribing, including the assessment of the risk of potential substance use disorder, pre- and post-intervention assessment of pain and pre- and post-intervention assessment of function.

In summary
Large-scale medical use of pregabalin in other countries during the last decade provides a significant amount of insight into potential misuse. New Zealand has been fortunate to avoid similar problems due to restricted use. The approval for funding means that potential prescribers need to be acutely aware of the risk of pregabalin misuse.

Competing interests:
Nil.

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REFERENCES: