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CURRENT OPINION

Misuse and Abuse of Pregabalin and Gabapentin: Cause for Concern?

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Abstract Gabapentinoids (e.g. pregabalin and gabapentin) are widely used in neurology, psychiatry and primary healthcare but are increasingly being reported as possessing a potential for misuse. In fact, increasing levels of both prescriptions and related fatalities, together with an anecdotally growing black market, have been reported from a range of countries. This article reviews the current evidence base of this potential, in an attempt to answer the question of whether there is cause for concern about these drugs. Potent binding of pregabalin/gabapentin at the calcium channel results in a reduction in the release of excitatory molecules. Furthermore, gabapentinoids are thought to possess GABA-mimetic properties whilst possibly presenting with direct/indirect effects on the dopaminergic 'reward' system. Overall, pregabalin is characterized by higher potency, quicker absorption rates and greater bioavailability levels than gabapentin. Although at therapeutic dosages gabapentinoids may present with low addictive liability levels, misusers' perceptions for these molecules to constitute a valid substitute for most common illicit drugs may be a reason of concern. Gabapentinoid experimenters are profiled here as individuals with a history of recreational polydrug misuse, who self-administer with dosages clearly in excess (e.g. up to 3–20 times) of those that are clinically advisable. Physicians considering prescribing gabapentinoids for neurological/psychiatric disorders should carefully evaluate a possible previous history of drug abuse, whilst being able to promptly identify signs of pregabalin/gabapentin misuse and provide possible assistance in tapering off the medication.

Key points

Gabapentinoids are thought to possess GABA-mimetic properties, whilst possibly presenting with direct/indirect effects on the dopaminergic 'reward' system.

Gabapentinoid experimenters are profiled here as individuals with a history of recreational polydrug misuse, who self-administer with dosages clearly in excess (e.g. up to 3–20 times) of those that are clinically advisable.

Physicians considering prescribing gabapentinoids for neurological/psychiatric disorders should carefully evaluate for a possible previous history of drug abuse, whilst being able to promptly identify signs of pregabalin/gabapentin misuse and provide possible assistance in tapering off the medication.

1 Introduction

Gabapentinoids (e.g. pregabalin and gabapentin; [1]) are widely used in neurology, psychiatry and primary healthcare. Both are anticonvulsants, with pregabalin being more recently introduced and structurally related to gabapentin.

Pregabalin has been identified within the 30 most prescribed medications in the USA in 2011 [2]. In Europe,

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pregabalin is approved for the treatment of epilepsy (partial seizures), neuropathic pain and generalised anxiety disorder. In the USA, although not approved for anxiety, pregabalin is further approved for fibromyalgia and postherpetic neuralgia [3]. The molecule is however also often prescribed off-label for a range of clinical conditions, including: bipolar disorder; alcohol/narcotic withdrawal states; attention-deficit/hyperactivity disorder; restless legs' syndrome; trigeminal neuralgia and non-neuropathic pain disorders [4]. In the USA, gabapentin is approved for the adjunctive treatment of complex epilepsy and postherpetic neuralgia in adults [5]. In the UK, the molecule is indicated for the treatment of both partial seizures and peripheral neuropathic pain [6].

Both pregabalin and gabapentin are increasingly being reported as possessing a potential for misuse [1, 7]. In the UK, for example, pregabalin and gabapentin prescribing has increased, respectively, by 350 and 150 % in just 5 years [8]. In Norway, Persheim et al. [9] analysed changes for the period 2008–2011 in the drug reimbursement system relating to expenditures for potentially addictive drugs in patients with severe/non-malignant chronic pain, and found that about one-third of the approved applications were for pregabalin. In parallel with this, there is an anecdotally growing black market, with gabapentinoids being allegedly available without prescriptions through online pharmacies [10]. In line with this, pregabalin and gabapentin first emerged in the UK mortality databases in 2006 and have shown an increasing trend since then in respect of being implicated in death. Indeed, most gabapentin victims (e.g. two-thirds in 2012) were not being prescribed with the molecule [11]. Similar findings have been reported from other countries, including: the USA [12]; France [13]; and Finland [14].

The aim of this 'current opinion' is to review and comment on the evidence relating to the existence of gabapentinoid potential for misuse, an issue of clear interest for prescribers and health professionals alike.

2 Methods/Literature Search Strategy

A literature search was conducted on key resources including PubMed, together with a focused Internet search for the identification of both existing prescribing guidelines and remaining relevant documents. When available, data from systematic reviews and randomised controlled trials were used. No filters were applied to limit the retrieval by study type, although there was a specific focus on human population data. The search was not restricted to English language documents only. Personal archives of references have been used as well, and consultation with experts to inform this manuscript has occurred.

3 Gabapentinoid Pharmacodynamics/Clinical Pharmacological Issues

Gabapentinoids decrease central neuronal excitability by binding to the auxiliary α2-δ protein/subunit of voltage-gated calcium channels on neurons [15–17]. The entry of calcium ions into neurons allows the process of vesicle fusion with cell membrane/release of neurotransmitters. Hence, potent binding of pregabalin/gabapentin at the calcium channel of hyperexcited neurons results in a reduction in the release of excitatory molecules [18], including: glutamate, noradrenaline and substance P [17]. Although pregabalin does not bind to the receptor, is not converted into GABA, nor does it alter GABA uptake or degradation, it is thought to possess GABA-mimetic properties [19]. Similarly, at relevant clinical concentrations, gabapentin does not bind to $GABA_A$, $GABA_B$, benzodiazepine or glycine/NMDA receptors [4]. Gabapentin may exert its GABAergic effects through both modulation of GABA metabolism and reversal of neuronal/glial amino acid transporters, with GABA being released for interaction with extra-synaptic GABA receptors [20, 21]. Indeed, gabapentin 900-mg administration to healthy human subjects resulted in an average increase in GABA concentration of about 56 % (6.9–91.0 %), with drug-induced changes in GABA levels being inversely correlated to the individual's baseline GABA levels [22]. Finally, it has been hypothesized that both gabapentin [22] and pregabalin [23] may somehow present with direct/indirect effects on the dopaminergic 'reward' system, effects that are typically associated with drugs' addictive liability levels [24].

At dosages exceeding the therapeutic dosages, gabapentinoids, different from clonazepam (e.g. a powerful benzodiazepine compound that may be misused; [25]), seem to anecdotally possess both *sedative* as well as *dissociative/psychedelic* effects [10]. This may be considered an observation that is in apparent contrast with gabapentinoids, similar to benzodiazepines, being GABA analogues only [26]. With a relatively short half-life of about 6 h, gabapentinoids are mostly (>98 %) excreted unchanged in the urine [15], with a urine specimen being positive for pregabalin for up to 5–6 days after intake in subjects with normal renal function [2].

3.1 Pregabalin vs. Gabapentin

Although pregabalin does interact with the same binding site and has a similar pharmacologic profile as gabapentin [16], its binding affinity for the α2-δ subunit, and potency, is six times more than that of gabapentin [27]. Furthermore, orally administered pregabalin is absorbed more rapidly than gabapentin, with maximum plasma concentrations

attained within 1 h as opposed to 3–4 h [15]. Indeed, the absolute bioavailability of gabapentin drops from 60 to 33 % as the dosage increases from 900 to 3,600 mg/day, while the absolute bioavailability of pregabalin remains at ≥90 % irrespective of the dosage [15]. One could conclude from here that distinct pharmacokinetic advantages of pregabalin over gabapentin may translate into an improved therapeutic effect [5], but may explain as well why pregabalin is anecdotally perceived as more 'powerful' by drug misusers [10, 28].

4 Gabapentinoid Potential for Misuse; the Available Evidence

At the time of marketing authorisation, following both preclinical/clinical studies' findings and no indication of significant dose escalation in open-label trials, the addictive liability levels of pregabalin were assessed to be low [29]. In line with this, Zacny et al. [30] aimed at characterising the subjective effects of pregabalin 75 and 150 mg in a double-blind randomized trial with 16 healthy volunteers. Abuse liability-related subjective effects such as drug liking/desire to take the drug again were not increased by either pregabalin dose. However, the authors acknowledged that their findings' generalisability was limited by the therapeutic/limited dosages chosen and the population selected (e.g. non-drug-abusing volunteers).

4.1 General Population Surveys

In analysing reports of possible drug abuse/addiction in the Swedish adverse drug reactions' national register, Schwan et al. [29] calculated the information component for pregabalin. Out of 198 reports indicative of abuse/addiction to any drug, 16 concerned pregabalin, and 13 of these patients reported a history of substance abuse. Bodén et al. [31] carried out a cohort study based on data extracted from Swedish national registers, including 48,550 patients who had been dispensed (2006–2009) with at least three prescriptions of pregabalin. They found that 8.5 % of these patients were dispensed a dose that exceeded the maximum daily allowance, with a previous drug misuse history having been identified in 31 % of this specific sub-sample. Similarly, Dyrkorn et al. [32] carried out in Norway a nationwide drug screening investigating 1,854 urine specimens, managing to identify pregabalin in 4.5 % of these samples. Finally, in a UK-based, anonymous, 1,500-respondent, online survey, Kapil et al. [26] compared misuse of baclofen, gabapentin and pregabalin. Respondents' self-reported lifetime prevalence of gabapentin misuse (1.1 %) was similar to pregabalin (0.8 %) and baclofen (1.3 %), in contrast with an alleged lifetime prevalence of cocaine and cannabis use, respectively, of 8.1 and 28.1 %. Frequency of misuse of these molecules was monthly in 37 % of cases and between once per month and once per week in 50 %.

4.2 Addiction Clinics' Surveys; Results from Online Data Analysis

A range of recent reports have emphasised the potential of gabapentinoids' misuse in selected populations. Pregabalin was detected in 12.1 % ($n = 15$) of urine samples from opiate-addicted subjects attending a German addiction clinic. None of these patients were suffering from any of the indications for pregabalin prescribing, with most having confirmed that they had acquired pregabalin illicitly whilst being well aware that the molecule was not included in the standard drug monitoring system [2]. Similarly, Baird et al. [33] carried out a questionnaire-based survey in six Scottish substance misuse clinics; 22 % (29/129) of respondents admitted to abusing gabapentinoids, with 38 % (11/29) of these clients abusing these molecules to potentiate the 'high' they obtained from methadone. In Tayside/Scotland, gabapentin/'gabbies' is available at the price of £1 (e.g. 1.2 euros/$1.66 USD) per 300-mg tablet, and may be used as a 'cutting agent' in street heroin [34]. Anecdotal data from south England inform that pregabalin is widely traded in prisons; that a number of clients of the needle exchange schemes are abusing pregabalin, and that this molecule is in some cases being preferred to heroin [28].

According to a qualitative overview of a range of online posts/notes/observations [10], a range of experiences may be associated with gabapentin abuse, including: euphoria, improved sociability and a marijuana-like 'high'/relaxation, but also 'zombie-like' effects [34]. A sedative/'opiate buzz' and psychedelic/3,4-methylenedioxy-N-methylamphetamine-like effects [10] are being reported as well. A few drugs are reportedly misused in combination with gabapentin, including: cannabis; alcohol; selective serotonin reuptake inhibitors; lysergic acid diethylamide (LSD); amphetamine; and gamma-hydroxybutyrate (GHB) [10]. Similarly, pregabalin is considered an 'ideal psychotropic drug' for recreational purposes to achieve specific mindsets, including: alcohol/GHB/benzodiazepine-like effects mixed with euphoria; to achieve entactogenic feelings/disassociation; and to cope with opiate/opioid withdrawal. Misuse of pregabalin, at dosages up to 20 times higher than the maximal dosage indicated [35], mostly seems to occur orally, but intravenous, rectal ('plugging'), smoking and 'parachuting' (emptying the content of the capsule into a pouch) self-administration techniques are also being reported [10]. Pregabalin is reportedly often taken in combination with other compounds, such as: alcohol/

gabapentin/benzodiazepines; cannabinoids/LSD/Salvia divinorum; heroin/opiates; and amphetamines/synthetic cathinones [10]. Abrupt/rapid discontinuation of high dosages of pregabalin is reportedly associated with withdrawal signs/symptoms (e.g. insomnia, nausea, headache or diarrhoea) and tolerance may reportedly develop fairly rapidly to quickly wear off upon drug cessation (for a review, see [10]).

4.3 Gabapentinoids as a Treatment for Addiction?

Pregabalin, at therapeutic daily levels, may present with beneficial effects for both alcohol withdrawal symptoms [36] and alcohol relapse prevention, with data on the maintenance of abstinence being similar to those associated with naltrexone prescription [37, 38]. Additionally, pregabalin has been shown to be effective in the withdrawal phase of both benzodiazepine [39] and opiate [40] detoxification, with valuable effects on cue- and stress-induced cocaine relapse [19]. Similarly, gabapentin has been indicated for the treatment/management of drug (e.g. opiates [41]; cannabis [42]), behavioural [43] and alcohol [44] addictions.

5 Discussion

We have reviewed the available evidence relating to pregabalin and gabapentin addictive liability levels. Overall, it seems that the risk of the misuse of gabapentinoids, if administered at therapeutic dosages to subjects who do not present with a substance misuse history [5, 30], may be lower than that of a range of other drugs, including: benzodiazepines [3]; remaining prescription medicines (e.g. opioids and stimulants) and alcohol/illicit drugs [45].

In contrast with this, however, some of the issues identified here may be a cause for concern, and these include: the complex gabapentinoid pharmacodynamics, possibly including the involvement of drug reward pathways [22]; the increasing prescription levels over time [8]; the misusers' perceptions for these molecules to constitute a valid substitute for most common illicit drugs [33]; and the increasing levels of associated fatalities from a range of countries [11]. Overall, gabapentinoid experimenters are profiled here as individuals with a history of recreational polydrug misuse [46] who self-administer with dosages clearly in excess (e.g. up to 3–20 times) of those that are clinically advisable [10, 35].

It is interesting to note that pregabalin has been approved in Canada and the USA since 2005, and approval by the European Commission to treat generalised anxiety disorder was received in 2006 [5]. Yet, the debate regarding abuse and dependence did not appear in the medical literature before 2010 [47, 48]. Similarly, remaining prescription drugs with misuse potential (e.g. benzodiazepines; z-hypnotics) were considered 'safe' for many years before their addictive liability levels were identified [49]. This may be because of pre-marketing clinical trials typically involving the administration of carefully controlled, daily therapeutic dosages. Furthermore, it is a well-known weakness of these trials that subjects with addiction disorders are excluded [29]. As a consequence, the real potential of misuse of the index molecule will be more properly appreciated only when a large number of clients, who will involve vulnerable individuals, are exposed to the drug.

A better assessment/clarification of gabapentinoid misuse potential levels is indeed of interest. In fact, in contrast with abuse liability data, pregabalin may potentially represent a valuable asset in the pharmacological repertoire of addiction medicine [17, 37]. Because gabapentinoids are commonly prescribed medications, health professionals should be well aware of both the potential risks for their misuse and the associated discontinuation symptoms. Physicians considering prescribing gabapentinoids for neurological/psychiatric disorders should carefully evaluate a possible previous history of drug abuse. Furthermore, they should be able to promptly identify signs of pregabalin/gabapentin misuse, whilst providing assistance in tapering off the medication [50].

The epidemiology of gabapentinoid misuse needs further detailed and urgent assessment, and consideration of gabapentin/pregabalin testing in urine drug screens should be routinely considered. Further empirical studies with gabapentinoids should be encouraged, focusing on a better assessment of their addictive liability levels across a range of dosages and in individuals with a previous substance misuse history [5].

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