A decade of gabapentinoid misuse: an analysis of the European Medicines Agency's 'suspected adverse drug reactions' database.

Assessment of gabapentinoid misuse/dependence as reported to the EMA.

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Abstract

INTRODUCTION: The gabapentinoids pregabalin and gabapentin are being increasingly prescribed for a range of clinical conditions. Recently, although gabapentinoids at therapeutic dosages may present with low addictive liability levels, cases of misuse and rising numbers of related fatalities have been reported.
OBJECTIVES: The aim of the study was to identify and assess cases of gabapentinoid misuse or dependence as reported to the European Medicines Agency's EudraVigilance (EV) database, in order to identify the magnitude of this problem and the characteristics of these reactions.
METHODS: All spontaneous reports of both gabapentin- (2004-2015) and pregabalin- (2006-2015) related misuse/abuse/dependence were retrieved. A descriptive analysis by source, sex, age, and type of report was performed.
RESULTS: From the EV database 7,639 (6.6% of a total of 115,616), and 4,301 (4.8% of 90,166) ADR reports of misuse/abuse/dependence were, respectively, associated with pregabalin and gabapentin, with an overall reporting frequency increasing over time. For both molecules, subjects typically involved were adult females. A total of 27 and 86 fatalities, respectively, associated with pregabalin and gabapentin, and mostly in combination with opioids, were identified. Analysis of proportional reporting ratios (PRR) for drug abuse/dependence/ intentional product misuse values seem to indicate that these ADRs were more frequently reported for pregabalin (1.25; 1.39; 1.58, respectively) compared to gabapentin.
CONCLUSIONS: Despite data collection/methodological approach limitations, the present data seem to suggest that gabapentinoid misuse may be a cause for concern, especially in patients with a history of substance misuse. Hence, healthcare professionals should be vigilant when prescribing these molecules.

Key points:
- Consistent with increasing levels of prescriptions and rising numbers of related fatalities, pregabalin and gabapentin have recently been reported as possessing addictive liability. Misusers may ingest these molecules in order to achieve euphoric/dissociative effects.
- The present study aimed to identify and assess cases of gabapentinoid misuse/dependence as reported to the EMA's EudraVigilance (EV) database.
-Despite data collection/methodological approach limitations, the present data suggest that gabapentinoid misuse may be a cause for concern, especially in patients with a history of substance misuse.

1. INTRODUCTION

The gabapentinoids pregabalin and gabapentin were originally developed as anticonvulsants and are now increasingly [1] and widely prescribed for a range of clinical conditions [2]. Recently, however, both drugs have been reported as possessing a distinct potential for misuse [3-8]. Although gabapentinoids at therapeutic dosages may present with a low addictive liability potential, misusers may ingest these molecules in order to achieve euphoric and dissociative effects similar to those of traditional recreational drugs [9-15].

Pregabalin is authorized in the European Union for epilepsy, neuropathic pain, and generalized anxiety disorder [16], with fibromyalgia being considered an additional indication in the US [17]. Pregabalin can also be effective in the treatment of benzodiazepine dependence, post-traumatic stress disorder, and alcohol dependence, even though it is not currently approved for the treatment of these conditions [2; 18]. In the US, pregabalin is a Schedule V drug (e.g. drugs with limited potential for abuse) [19]. However, signals for the dependence potential of pregabalin were identified as early as 2004 in the UK [20] and in 2005 worldwide [21], with overall cases progressively increasing since 2008 [22]. History of substance misuse is typically associated with overuse of pregabalin [23-26]. Although tolerance to pregabalin has not been proven [27-28], its withdrawal syndrome may include agitation/anxiety, craving, sweating, insomnia, fatigue, palpitations, tremors, and diarrhoea [29-33].

Gabapentin is approved to treat epilepsy and neuropathic pain disorders [4; 34], with off-label use of the molecule including restless legs syndrome, migraine, vasomotor symptoms of menopause, and alcohol and substance dependence [2; 35-38]. There are anecdotal reports of its misuse [39], particularly in cocaine users and prison settings [40-41]. A gabapentin withdrawal syndrome, with features similar to those reported with pregabalin, has been described [42-43].

Gabapentinoids selectively bind to the α2-δ subunit of voltage-gated calcium channels in central nervous system neuronal tissues. As a result, GABA levels increase in parallel with the inhibition of the release of excitatory neurotransmitters, possibly accounting for the antinociceptive, anticonvulsant, anxiolytic, and sleep-modulating activities of gabapentinoids [44]. It remains to be confirmed if gabapentinoid ingestion is associated with meaningful levels of dopamine reward pathway activation [45-46]. Even though pregabalin and gabapentin share similar mechanisms of action, they differ in their pharmacokinetic and pharmacodynamic characteristics. Indeed, pregabalin binding affinity for the α2-δ subunit, and potency, is six times higher than that of gabapentin. The putative higher addiction potential of pregabalin in comparison with gabapentin may be due, as well, to a range of factors, including more rapid absorption, faster onset of action/attainment of maximum plasma concentration [47], and higher bioavailability, which remains at >90% irrespective of the dosage (for a review, see [48]).

The European Medicines Agency (EMA) is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed for use in the European Union (EU). The EMA coordinates the EU pharmacovigilance system, including managing the EudraVigilance (EV) [49] database since 2001. The EV database is the central database of electronic reports of suspected adverse drug reactions (ADRs) for all medicinal products authorised in the European Economic Area (EEA; including 28 European countries together with Iceland, Liechtenstein and Norway [50]). ADRs are reported to the EV database by Regulatory Authorities of the Member States where the reaction occurred, as well as by the Marketing Authorisation Holders for ADRs occurring outside the EEA. The suspected ADRs originate from 'spontaneous case reports', defined as follows: 'an unsolicited communication by a healthcare professional, or consumer, to a competent authority …. that describes one or more suspected adverse reactions in a patient who was given one or more medical products ….' [51].

The aim of this study was to identify and assess cases of gabapentinoid misuse, abuse or dependence reported to the EMA's EV database, in order to identify the magnitude of this problem and the characteristics of these reactions.

2. METHODS

Following a formal request, the EMA allowed us to access the tabulated information available from the EV database on case reports of pregabalin- and gabapentin- related ADRs. Search periods for pregabalin and gabapentin differed because they presented with different approval/commercial availability times.

The EV database defines an ADR as 'an undesirable effect, a response to a medicinal product which is noxious and unintended'. The EV database also considers 'reporting' as a causal relationship between a medicinal product and an adverse event which is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors. Data in the EV system are coded against the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) [51]. ADRs are listed by 'Preferred Terms' (PTs) and grouped by 'System Organ Class' (SOC) of the Medical Dictionary for regulatory Activities (MedDRA), supporting the coding of adverse reactions [52]. Within the standardised MedDRA Query (SMQ) 'drug abuse, dependence and withdrawal' section, we identified the following adverse reactions associated with gabapentin and pregabalin: 'drug abuse', 'drug abuser', 'drug dependence', 'intentional product misuse', 'intentional product use issue', 'polysubstance dependence', 'substance abuse', 'substance abuser', and 'drug withdrawal syndrome'. In accordance with MedDRA definitions [53], we referred here to 'misuse' as the intentional and inappropriate use of a product other than as prescribed or not in accordance with the authorized product information. Conversely, 'abuse' is the intentional, non-therapeutic, use of a product for a perceived reward or desired non-therapeutic effect including, but not limited to, 'getting high'/euphoria. Finally, 'addiction' (typically replaced by 'dependence' [54]), is here the overwhelming desire to take a drug for non-therapeutic purposes together with inability to control or stop its use despite harmful consequences.

In the analysis here performed, the number of ADRs could be different from the number of case reports as one case report may refer to several ADRs. Furthermore, different reporters/senders could have independently signaled the ADR to the EMA. Within the EV database, the *reporter* is the primary source of the information, i.e. the person who actually reports the facts. The reporter is identifiable by name, initials, address, and qualifications (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-health professional), although local data privacy laws regarding both patient and reporter identity might typically apply. Conversely, the *sender* is the person or entity creating the message for transmission, with the reporter and the sender being at times the same person. Each case/individual patient in the database has a code (EV local number) for identification. Hence, the number of cases or individual patients was unequivocally identified counting the number of values in the EV local number column of the ADRs' database using a worksheet function. The EV database considers the 'drug role' as the assessment of the relationship between respectively pregabalin or gabapentin prescription and the reported observation of abuse/dependence.

Cases were analysed considering a range of parameters, including: age and gender of the patient; source/reporter country; sender type; reporter qualification; outcome(s); concomitant drug(s); and drug's role. Two different 'line listings', one for each drug, were received via EudraLink, e.g. a secure electronic system. The databases discussed include all case reports submitted as 'spontaneous' to the EV database up to mid-July 2015.

To more properly compare pregabalin vs gabapentin, the proportional reporting ratios (PRR) approach was here considered as well. This is a measure of disproportionality of reporting used to detect ADRs in pharmacovigilance databases such as the EV. A PRR greater than 1 suggests that

the adverse event is more commonly reported for individuals taking the drug of interest, relative to the comparison drug(s). The PRR is defined as the ratio between the frequency with which a specific adverse event is reported for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event is reported for the drug(s) in the comparison group (relative to all adverse events for drugs in the comparison group).
The PRR is computed as follows: $\frac{A/A+B}{C/C+D}$
(where: A is the number of individual cases with pregabalin involving the adverse events drug abuse/drug dependence/intentional product misuse; B is the number of individual cases related to pregabalin involving any other adverse events; C is the number of individual cases involving the events drug abuse/drug dependence/intentional product misuse in relation to gabapentin; and D indicates the number of individual cases involving any other adverse events associated with gabapentin) [55].
All EV database suspected ADR case reports here discussed have been partially redacted in accordance with Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data.

3. RESULTS

For both pregabalin and gabapentin, most reports originated from north America, followed by east Asia and south America, whilst EEA pharmaceutical companies represented the most typical senders. The drug role was typically considered to be 'suspect'.

3.1 PREGABALIN ADRs

Over the period 03/2006-15/07/2015, the EMA received 115,616 ADRs reports relating to pregabalin; this molecule had been approved by the EMA in 2006, when gabapentin was already available. Out of these, 7,639 reports were relating to abuse/dependence/product misuse issues, corresponding to 1,315 patients and 6.61% of all ADRs recorded. The number of reports increased consistently year-per-year (Figure 1), with a peak in 2013 (2,154 reports) and a decrease in 2014 (1,593 reports), reaching 1,387 by July 15th, 2015. Using the SMQ terms, 32.2% were classified as 'intentional product misuse', 31.9% as 'drug dependence', and 22.3% as 'drug abuse'. Overall, typical subjects here involved were adult females (F/M ratio: 1.13/1), although a gender uneven distribution was seen as well in all ADRs reports (F/M ratio: 3.08/1). Index drugs reported to be most concurrently misused in combination with pregabalin included opioids (identified in n=791; 10.35% of ADRs), antidepressants and benzodiazepines.

3.2 GABAPENTIN ADRs

Over the period 03/2004-15/07/2015, the EMA received 90,166 ADRs reports relating to gabapentin. Out of these, 4,301 were relating to abuse/dependence issues, corresponding to 410 patients and 4.77% of all ADRs recorded. The number of reports increased consistently year-per-year (Figure 1). Using the SMQ terms, 28.3% were classified as 'intentional product misuse'; 31.8% as 'drug dependence'; and 24.8% as 'drug abuse'. Overall, typical subjects involved here were adult females (F/M ratio: 1.27/1), although a gender uneven distribution was seen as well in all ADRs reports (F/M ratio: 2.1/1). Index drugs reported to be most concurrently misused with gabapentin were opioids (identified in n=555; 12.9% of ADRs), antidepressants and benzodiazepines.

3.3 PREGABALIN VS GABAPENTIN; PRR COMPUTATION

Table 1 presents the data relating to 'pregabalin vs gabapentin' PRR calculations whilst considering the three most represented ADRs, e.g. drug abuse; drug dependence; and intentional product misuse.

The resulting PRR values suggest that these ADRs were more frequently reported for pregabalin (respectively: 1.25; 1.39; 1.58) compared to gabapentin. As an example, the PRR for A1/drug abuse has been computed as follows:

$$\frac{A1/A1+B}{C1/C1+D} = \frac{1706/(1706+109007)}{1066/(1066+86513)} = \frac{0.015}{0.012} = 1.25$$

3.4 RELATED FATALITIES

In the 1,315-patient pregabalin group, 27 (2.05%) fatality reports were identified, but only in 5 cases the drug was reported on its own. Thirteen cases involved adult females, and 10 cases had occurred in 2014. Most reports were sent by a physician (10 cases) and originated from outside the EEA (11 cases).

Conversely, in the 410-patient gabapentin group, 86 (21%) fatalities were identified and in 3 cases gabapentin was reported on its own. Fifty-one cases involved adult females, and 23 cases had occurred in 2014. Most (78 cases) reports originated from outside the European area.

In association with pregabalin and gabapentin, opioids were the concomitant drugs most typically identified, followed by antidepressants and benzodiazepines. A range of recreational substances (e.g. alcohol, amphetamines, cannabis, and ketamine) was at times identified as well.

4. DISCUSSION

To the best of our knowledge, this is the first and largest scale study aimed at identifying and analysing gabapentinoid misuse/dependence issues as reported to a pharmacovigilance database such as the EMA's EVdatabase. This database, together with the WHO's Drug Monitoring Programme [56], is considered a world-wide reference standard [57]. As expected, EEA pharmaceutical companies were identified as the most typical spontaneous reporters.

Overall, 7,639 (6.6% out of a total of 115,616), and 4,301 (4.8% of 90,166) ADR reports were, respectively, relating to pregabalin and gabapentin abuse/dependence issues. These figures are somewhat higher than those extracted from a German database query, which reviewed any pregabalin-related ADRs and found that 55 of 1,552 reports (3.5%) related to pregabalin abuse/dependence issues [58]. Regarding gabapentin, very recent reports have highlighted that 20% of patients in treatment may misuse/abuse with this molecule and that accident and emergency visits involving the nonmedical use of gabapentin have increased by 90% in the United States since 2008 [59].

The PRR values that we calculated suggested that abuse/dependence issues were more frequently reported for pregabalin compared to gabapentin. This may be explained by a range of contributory factors, including higher addictive liability of pregabalin in comparison to gabapentin [4], and a larger range of clinical conditions being considered by clinicians in choosing between pregabalin and gabapentin. Indeed, apart from neuropathic pain, pregabalin can be prescribed for anxiety as well, a condition which has in turn been associated with a vulnerability to addiction [60-61]. Hence, different from gabapentin, with pregabalin there are more chances of prescribing to subjects who are psychologically vulnerable/arguably more prone to substance misuse.

The present data may support the idea of overall increasing levels of gabapentinoid misuse reports over time, a narrative consistent with previous observations made with traditional psychoactives, e.g. benzodiazepines. These molecules were considered safe for many years before their addictive liability levels were identified [62].

Overall, the female gender was more represented in all ADRs received by the EMA, including the abuse/dependence cases. Indeed, excluding epilepsy [63], gabapentinoids are prescribed to treat disorders which are more typically identified in females, including chronic/neuropathic pain [64], generalized anxiety disorder [65], fibromyalgia [66], restless legs syndrome [67], migraine [68] and, of course, vasomotor symptoms of menopause.

In the EV database, 27 pregabalin- and 86 gabapentin-related fatality reports were identified. Although this finding is in itself interesting, to be able to calculate properly the gabapentinoid 'fatal toxicity index' [69] one would need to have the total number of patients exposed to either pregabalin or gabapentin. In contrast to pregabalin, which has already been extensively identified in forensic toxicological analysis [6], gabapentin acute toxicity/morbidity incidents have previously been identified only in patients with a compromised renal function [70-71]. In the UK, overall, the number of post-mortem cases in which gabapentinoids were implicated has progressively increased since 2006 [5]. Consistent with the present data, opioids and alcohol were identified in 90% and 15%, respectively, of gabapentinoid-related fatalities that occurred during 2010-2011 in Finland [72]. Similarly, opioids were implicated in most (66%) overdose-related deaths involving antiepileptics in the US [73]. Opioids may have been prescribed here to potentiate gabapentinoid analgesic effects for treating specific medical conditions/intractable pain. However, gabapentin bioavailability may increase by 50% when co-administered with morphine [48]. Furthermore, gabapentinoids contribute to the elderly sedative load and corresponding risk of falls [74]. Finally, gabapentinoids may be ingested by opioid addicts to potentiate the substitute opiates/opioids' psychoactive effects [75-78].

5. LIMITATIONS

Case reports of suspected ADRs alone are rarely sufficient to confirm that a certain effect in a patient has been caused by a specific medicine. The fact that a suspected adverse reaction has been reported does not necessarily mean that the medicine has caused the observed effect, as this could have also been caused by the disease being treated, a new disease the patient developed, or by another medicine that the patient is taking. Furthermore, the number of case reports for a particular medicinal product depends as well on its availability in the market and its extent of use, the nature of the reaction and public awareness of a safety concern. Hence, comparing the number of case reports between medicines may give a misleading picture of their safety profiles. Furthermore, spontaneous reports were likely to reflect here issues relating to prescribed gabapentinoids only, whilst these molecules are widely available from rogue websites [14] and, in some countries, over-the-counter as well.

It appears from our data that there were a number of ADRs relating to the same patient. This may have happened because of a range of different sources reporting the same ADR but also because for the same patient a number of different ADRs may have been reported. Furthermore, full levels of information regarding the subjects' possible psychiatric/drug misuse history were not available, and the gabapentinoid abuse/dependence diagnosis was not made in accordance with international classifications standards. Overall, both reporting and publication bias may have occurred. In fact, the recently increasing number of literature papers highlighting the addictive liability of gabapentinoids [4] may have facilitated the related spontaneous reporting levels. Finally, a PRR exceeding 1 could also reflect sampling variation in the data, reporting errors, biased reporting, multiple reports of the same case or the same patient, or a number of other causes.

6. CONCLUSIONS

Despite data collection limitations, the data presented in this paper seem to confirm the misuse potential of gabapentinoids. Whether or not this misuse is occurring on a large scale cannot be confirmed from our data. As the EV database reports were submitted spontaneously, present figures may however represent an underestimate of the problem. Further, prospective, studies should be encouraged to better assess the addictive liability of gabapentinoids, particularly because these drugs are under investigation for the treatment of substance related disorders, specifically benzodiazepine and alcohol withdrawal [2]. Healthcare professionals should be vigilant when prescribing these molecules, particularly in both patients with a substance misuse history [4; 17; 79], and inmates [41; 80]. Due to the possibility of diversion, amount of drug prescribed per

individual prescription should be limited and, if any related misuse issues are identified, physicians should consider medication tapering.

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Conflicts of interest
Professor Schifano and Dr. Chiappini report no conflicts of interest with respect to the content of this manuscript; please note however that Professor Schifano is a member of the EMA Psychiatry Advisory Board.

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