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Gabapentin drug misuse signals: A pharmacovigilance assessment using the FDA adverse event reporting system

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ABSTRACT

Background: Although there have been increasing reports of intentional gabapentin misuse, epidemiological evidence for the phenomenon is limited. The purpose of this study was to determine whether there are pharmacovigilance abuse signals for gabapentin.

Methods: Using FDA Adverse Events Reporting System reports from January 1, 2005 to December 31, 2015, we calculated pharmacovigilance signal measures (i.e., reporting odds ratio, proportional reporting ratio, information component, and empirical Bayes geometric mean) for abuse-related adverse event (AR-AE)-gabapentin pairs. Loglinear modeling assessed the frequency of concurrent reporting of abuse-related and abuse-specific AEs (AS-AEs) associated with gabapentin. Findings were compared to a positive (pregabalin) and negative (duloxetine) control.

Results: From 2005–2015 there were 5,951,229 unique AE reports submitted to the FDA including 99,977 for gabapentin, 73,977 for duloxetine, and 97,813 for pregabalin. Significant drug-AR-AE pair signals involving gabapentin included: *drug abuser*, *multiple drug overdose*, and *substance-induced psychotic disorder*. Significant drug AR-AE signals involving gabapentin and pregabalin, but not duloxetine, were: *ataxia*, *dependence*, *drug abuse*, *increased drug tolerance*, and *overdose*. Compared to duloxetine, gabapentin had significantly greater odds of a co-report for an AS-AE with *drug withdrawal syndrome* (OR: 6.55), *auditory hallucinations* (OR: 4.57), *delusions* (OR: 2.36), *euphoric mood* (OR: 5.45), *ataxia* (OR: 2.85), *drug abuser* (OR: 3.01), *aggression* (OR: 1.98), *psychotic disorder* (OR: 1.96), and *feeling abnormal* (OR: 1.31).

Conclusions: We identified abuse-related signals for gabapentin and highlighted several CNS effects that may be associated with its abuse. Gabapentin prescribers should be aware of the drug's abuse liability and effects that may accompany its use.

1. Introduction

Gabapentin is approved by the U.S. Food and Drug Administration (FDA) for post-herpetic neuralgia and as an anti-epileptic, but is frequently used off-label for non-herpetic pain, mood disorders, and as a treatment for alcohol withdrawal and alcohol use disorder. In the latest guidance report for pain treatment, the Centers for Disease Control and Prevention (CDC) identified gabapentin as a first-line medication for treating chronic pain (Dowell et al., 2016). Since its market release in 1993, gabapentin was presumed to have no abuse potential, which has likely led to its extensive off-label prescribing (it is estimated that between 83–95% of all gabapentin prescriptions are for a non-approved

Abbreviations: AE, adverse event; AER, adverse event report; AR-AE, abuse related adverse event; AS-AE, abuse specific adverse event; C, concomitant drug; CDC, Centers for Disease Control; EBGM, empirical Bayesian geometric mean; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; I, interacting drug; IC, information component; ISR, individual safety report; MedDRA, Medical Dictionary for Regulatory Activities; PhV, pharmacovigilance; PRR, proportional reporting ratio; PS, primary suspect drug; PT, preferred term; ROR, reporting odds ratio; SS, secondary suspect drug

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use; Hamer et al., 2002; Radley et al., 2006). However, since the first published report of gabapentin misuse in 1994 (Fischer et al., 1994), a substantial number of accounts of gabapentin misuse and abuse have followed. A recent systematic review identified 23 published case studies and epidemiologic reports of gabapentin misuse/abuse from seven different countries (Smith et al., 2016).

Evidence on the prevalence of gabapentin misuse (i.e., use in a manner or for a purpose other than indicated) (World Health Organization, 2015a) is limited. One study estimated the population prevalence of gabapentin misuse at 1 % in the United Kingdom (Kapil et al., 2014). However, three studies estimated the prevalence of gabapentin misuse within substance misuse samples in the United States and the United Kingdom to be between 15–22% (Baird et al., 2014; Smith et al., 2015; Wilens et al., 2015). The mechanism by which gabapentin produces analgesic and anticonvulsant effects is unknown, though it is likely due to an interaction with calcium channels to reduce neurotransmitter release from neurons in the central nervous system (Bockbrader et al., 2010). There is a wide spectrum of subjective effects of gabapentin, particularly when it is not used as intended (e.g., in larger doses than prescribed), including: dissociation, euphoria, sedation/relaxation/calmness, elevated mood, disinhibition, delirium, feeling "high," and feeling drunk (Reeves and Burke, 2014; Reeves and Ladner, 2014; Satish et al., 2015; Schifano et al., 2011; Vickers Smith et al., 2018).

Without controlled pharmacological studies to assess gabapentin's abuse potential, other available data can be used to estimate the risk of gabapentin misuse. One such resource is the FDA Adverse Event Reporting System (FAERS), a publicly available, FDA- maintained database in the United States. FAERS is a passive surveillance program to which post-marketing adverse events (AEs) associated with any drug or biologic product can be reported. Approximately 5 % of AEs reported to FAERS are generated voluntarily by health professionals (e.g., physicians, pharmacists, nurses) and consumers (e.g., patients, family members, lawyers), who can submit AEs via the online submission system called MedWatch (U.S. Food and Drug Administration, 2016). The other 95 % of FAERS reports come from voluntary AE reporting to the drug sponsor or manufacturer, which is then required to forward the report to the FDA (U.S. Food and Drug Administration, 2016). The Center for Drug Evaluation and Research, a division of the FDA, monitors reports and further evaluates concerns identified through FAERS (Center for Drug Evaluation and Research, 2018a). If there is a safety concern over a drug or device, the FDA can choose to take regulatory action, including, but not limited to: updating labeling information, restricting use, communicating safety information to the public, or product removal from the market (Center for Drug Evaluation and Research, 2018a). As of 2016, FAERS has received over 12 million reports, two million of which were from 2016 alone (U.S. Food and Drug Administration, 2016).

Pharmacovigilance (PhV), which is the collection, study, detection, and prevention of drug adverse events, is a useful tool for hypothesis generation or hypothesis testing of drug-AE pairs, though a theoretical conceptualization of the drug-AE combination one intends to investigate is prerequisite (Poluzzi et al., 2012). PhV studies typically use several assessment measures to detect a "signal" for a particular drug (World Health Organization, 2015b), which is a previously unknown possible causal association of an adverse event resulting from taking a drug (World Health Organization, 2012). Signals are disproportionality measures based on a 2 × 2 contingency table and determine whether a drug-AE pair occurs more often than expected by comparing signal values to published thresholds (Bate et al., 1998; Evans et al., 2001; Szarfman et al., 2002; van Puijenbroek et al., 2002).

We used the FAERS database to calculate signal measures for reports of gabapentin and abuse-related AEs (AR-AEs) and compared these findings to a negative and positive control. The AR-AEs of interest were selected *a priori* based on effects associated with gabapentin misuse reflected in the current literature (Schifano et al., 2011; Smith et al., 2016). Signals of misuse/abuse/addiction may not always be identified through observation of a single AE at a time (e.g., a report of gabapentin and ataxia does not necessarily indicate abuse); rather, it may be more useful to examine the joint occurrence of several AEs that are indicative of drug misuse/abuse/addiction. Therefore, in addition to the traditional signal measures, we used loglinear modeling to assess the frequency of concurrent reporting of AEs associated with gabapentin misuse/abuse.

2. Material and methods

2.1. Data source

All FAERS quarterly data from January 1, 2004 to December 31, 2015 were downloaded from the FDA website (Center for Drug Evaluation and Research, 2018b). However, because pregabalin was not approved by the FDA until December 30, 2004 (U.S. Food and Drug Administration, 2005), data from 2004 were excluded. Each quarterly data set contained 7 data files: (1) patient demographic and administrative information; (2) drug/biologic information for all medications reported for the event; (3) all Medical Dictionary for Regulatory Activities (MedDRA) terms coded for the adverse event; (4) patient outcomes for the AE; (5) report sources for the AE; (6) drug therapy start and end dates for the reported drug(s); and (7) all MedDRA terms for the reported drug's indications/diagnoses. For the purposes of this analysis, only the demographic, drug, and reaction data tables were used.

We used positive and negative controls with which to compare the gabapentin findings. Pregabalin, a structural analog of gabapentin with a similar mechanism of action, has been classified as a Schedule V drug because of its abuse potential, which made it an ideal candidate for the positive control. Because duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been recommended as a first-line medication for the treatment of neuropathic pain (Dowell et al., 2016) (similar to gabapentin) but is not a controlled substance and generally has produced no signal of abuse liability, it was selected as the negative control.

Based on the proposed methodology of Moore et al. (1997) a case/non-case approach was used, where each drug-AE pair of interest denoted a case and all other possible pairs were non-cases. In every FAERS AE drug file, FDA clinical reviewers assigned role codes to each reported drug and indicated as follows: primary suspect drug (PS), secondary suspect drug (SS), interacting (I), or concomitant (C). Often, only PS, SS, and I medications are considered as cases. However, others have raised concerns about excluding concomitant medications from among cases, particularly if they are associated with an unexpected drug-AE association. As explained in the EudraVigilance data analysis guidelines, "…it is quite often the case that drug-event associations are not commonly established until knowledge of the potential signal [is] available" (European Medicines Agency, 2006). Therefore, due to the historic opinion that gabapentin had no abuse liability it was apt to include cases where gabapentin was listed as a concomitant medication. For consistency, cases where pregabalin or duloxetine were listed as concomitant medications were also included.

2.2. Case identification - drugs

Drug cases (i.e., AE reports [AERs] that included gabapentin, pregabalin, and/or duloxetine) were identified in the FAERS drug table using a phonetic algorithm via the soundex function in the R package, *phonics* (Howard, 2018). The soundex function was employed to identify potential drug case matches by both the brand and generic names of the case drugs. This procedure works through phonetic matching and can help to reduce the effect of variations in spelling. The second author manually scanned potential matches identified through the phonetic algorithm to determine whether they were true cases. All analyses were conducted in R.

2.3. Data cleaning

Each AER in FAERS has a unique "ISR (individual safety report) number," which can be used to link files across all seven data tables. A case number also identifies an AER; however, it may encompass several ISR numbers (AERs) due to follow-up reporting for the same event. Once the drug files were merged with their corresponding demographic files by ISR number, we retained the AER in each Case ID series with the most recent date, according to the FAERS cleaning protocol (Banda et al., 2016), and duplicates were removed. The demographic/drug file was then merged with the MedDRA AE file by the ISR number.

2.4. Case identification - AEs

Using several sources (Schwan et al., 2010; Smith et al., 2013), we created a list of MedDRA preferred terms (PT) that were explicit indications of abuse (e.g., drug diversion, drug addiction) and those that could be indicative of abuse (e.g., ataxia, falls, euphoric mood, dissociation). Here *abuse-related* (AR-AE) will be used to incorporate both explicit abuse MedDRA terms and MedDRA terms that are possible indicators of abuse, while *abuse-specific* (AS-AE) refers to explicit abuse terms only. The list was reviewed by a pharmacology expert [SLW] and a psychiatrist [MRL] and revised until a final list was agreed upon (see Appendix 1). It should be noted that each AER could, and most often did, include more than one MedDRA term.

2.5. Signal calculation

Because AE reporting can be affected by many external factors, cumulative signal measures were calculated (Poluzzi et al., 2012); that is, data were aggregated over the 11-year study period rather than calculated quarterly. Descriptive statistics were calculated for each drug-AR-AE pair. Traditional signal measures include the proportional reporting ratio (PRR)(Evans et al., 2001), reporting odds ratio (ROR) (van Puijenbroek et al., 2002), the information component (IC)(Bate et al., 1998), and the empirical Bayesian geometric mean (EBGM) (Szarfman et al., 2002). Published criteria for each signal measure are as follows (Poluzzi et al., 2012):

For N_D, which is the number of AERs for any given drug:

PRR: $N_D \geq 3$, PRR ≥ 2, $\chi^2 \geq 4$;

ROR: lower limit of 95 % confidence interval > 1;

IC: lower limit of two-sided 95 % credible interval > 0;

EBGM: $N_D > 0$, lower limit of one-sided 95 % credible interval > 2.

First, a composite AR-AE variable was created, that is, any AER that reported at least one of the AR-AEs was coded as 1 and AERs that did not report any of these AR-AEs were coded as 0. Signal measures were calculated for each drug-composite AR-AE pair. Then signal measures were calculated for individual AR-AE-drug pairs. Because the traditional signal measures differ in their sensitivity and specificity, we decided that for our purposes, a drug-AE pair would be significant if all four signal measures met the thresholds described above. The R package, PhViD (Ahmed and Poncet, 2016), was used to obtain all signal scores.

2.6. Loglinear analysis

Loglinear models allow for the simultaneous examination of the association between more than two categorical variables, essentially an extension of the 2×2 contingency table to a $2 \times 2 \times \ldots \times 2$ table, particularly useful when there is more than one response variable. This type of model can describe the joint distribution of any number of categorical factors.

First, a composite abuse-specific (AS-AE) variable was created where any AER that reported at least one AS-AE was coded as 1 and AERs that did not were coded as 0. The AS-AEs included: addiction, dependence, drug abuse, drug dependence, drug diversion, intentional (drug) misuse, intentional overdose, multiple drug overdose, overdose, prescription drug use without a prescription, substance abuse, and substance use. MedDRA terms drug abuser and substance abuser were not included as AS-AEs because those refer to the social circumstances surrounding the event. Therefore, information may be provided in the AER that the individual had a history of drug misuse, but that does not necessarily indicate that abuse occurred.

Next, loglinear modeling was used to evaluate the association between the co-occurrence of an AS-AE and each AE that was a possible indicator of abuse (e.g., ataxia, substance abuser) in AERs for gabapentin and pregabalin, with duloxetine as the referent group. All data were assumed to have come from Poisson distributions. Further, AERs that co-indicated any of the case drugs together (e.g., AER with gabapentin and pregabalin; AER with pregabalin and duloxetine) were not included in the loglinear analysis to reduce potential conflation of effects.

3. Results

From 2005–2015 there were 5,951,229 unique AERs submitted to the FDA. Of those, 99,977 included gabapentin, 73,977 included duloxetine, and 97,813 included pregabalin. Overall, the general trends for received AERs for each case drug were increasing, perhaps more clearly so for pregabalin and gabapentin than for duloxetine (Fig. 1). Interestingly, AERs for gabapentin, pregabalin, and duloxetine shared many of the same most frequently reported AEs including drug ineffectiveness, pain, nausea, fatigue and dizziness (Table 1).

Nearly one-quarter of all gabapentin reports involved at least one abuse-related AE (22.93 %; Table 2). That percentage was slightly higher for pregabalin and duloxetine (26.13 and 29.32 %, respectively). Of all the gabapentin-abuse-related AEs, dizziness was reported most frequently (5.25 %), followed by falls (4.48 %), and somnolence (3.33 %). Dizziness and somnolence were also the most frequently reported abuse-related AEs reported for pregabalin (6.59 % and 5.17 %, respectively), while dizziness (8.03 %), drug withdrawal syndrome (6.42 %), and feeling abnormal (5.26 %) were most common for duloxetine. With regard to AS-AEs, overdose was reported most frequently for all three drugs (gabapentin: 1.37 %; pregabalin: 0.94 %; duloxetine: 1.05 %). Also in the top five most commonly reported AS-AEs for all three drugs were: drug abuse (gabapentin: 0.57 %; pregabalin: 0.66 %; duloxetine: 0.37 %), intentional drug misuse (gabapentin: 0.55 %; pregabalin: 0.55 %; duloxetine: 0.58 %), intentional overdose (gabapentin: 0.50 %; pregabalin: 0.36 %; duloxetine: 0.51 %), and drug dependence (gabapentin: 0.49 %; pregabalin: 0.59 %; duloxetine: 0.29 %).

When examining signal measures of gabapentin, 30 gabapentin-AE pairs met published threshold criteria for all four measures (Appendix 2). Likewise, 32 pregabalin-AE pairs and 29 duloxetine-AE pairs met published signal threshold criteria for all four measures. Significant signals (i.e., using our more stringent definition) common to all three drugs included aggression, confusional state, disorientation, dizziness, drug dependence, drug tolerance, drug withdrawal syndrome, euphoric mood, fall, feeling abnormal, feeling drunk, gait disturbance, hallucination, visual hallucination, incoherent, intentional drug misuse, intentional overdose, mood altered, off-label use, somnolence, and thinking abnormal. Significant AE signals unique to gabapentin (i.e., not all 4 signals were significant for pregabalin or duloxetine) were: drug abuser, multiple drug overdose, and substance-induced psychotic disorder. Significant AE signals with gabapentin and pregabalin, but not duloxetine (i.e., not all 4 signals were significant for duloxetine), were: ataxia, dependence, drug abuse, drug tolerance increased, and overdose. Only delusion produced a significant AE signal with gabapentin and duloxetine, but not pregabalin. Gabapentin, pregabalin, and duloxetine produced significant signals for both the composite abuse-related AE variable and the abuse-specific AE variable. Each drug had AS-AEs that met the significance threshold for one or more of the PhV measures, but not for all 4. These included: dependence (duloxetine),

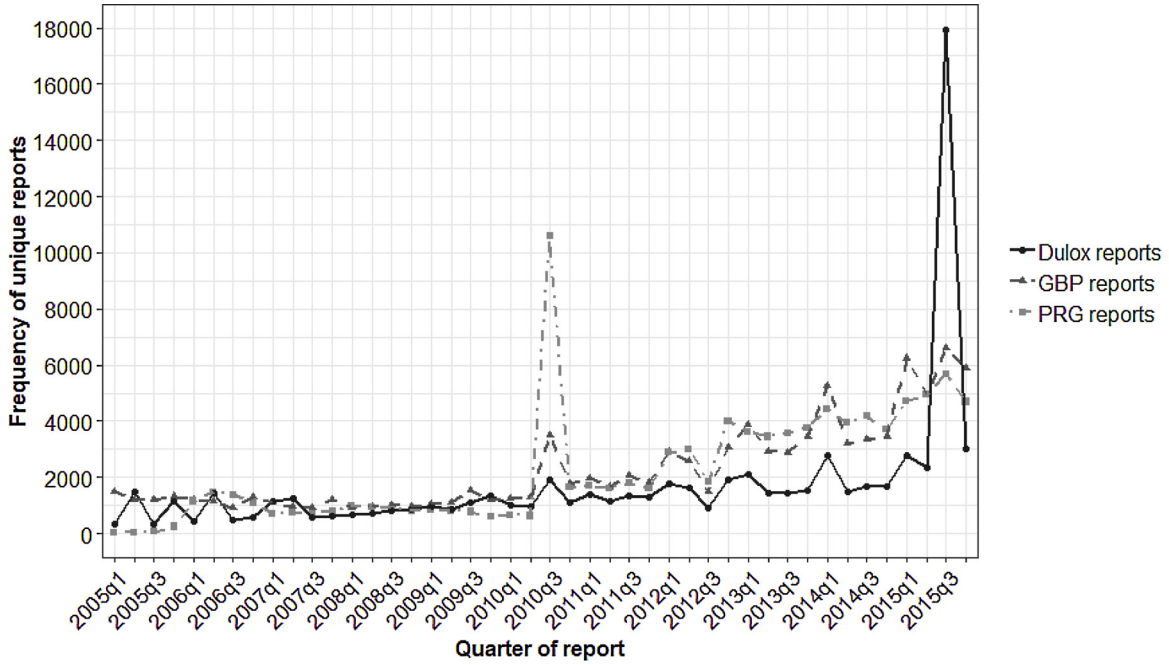

Fig. 1. Adverse reporting trends by quarter, 2005–2015.
Dulox = duloxetine; GBP = gabapentin; PRG = pregabalin

Table 1
Highest frequency of adverse events by drug, 2005–2015.

Gabapentin (n)	Pregabalin (n)	Duloxetine (n)
Drug ineffective (9913)	Pain (9962)	Nausea (7354)
Pain (6784)	Drug ineffective (9290)	Dizziness (5941)
Nausea (6341)	Dizziness (6444)	Headache (5069)
Fatigue (5690)	Weight increased (5764)	Drug ineffective (5016)
Dizziness (5251)	Somnolence (5059)	Fatigue (4825)
Headache (4838)	Nausea (4304)	Drug withdrawal syndrome (4752)
Fall (4479)	Malaise (4128)	Pain (4747)
Diarrhea (4408)	Pain in extremity (4055)	Insomnia (4132)
Dyspnea (4266)	Fatigue (3996)	Depression (4108)
Depression (3935)	Feeling abnormal (3952)	Feeling abnormal (3889)

drug abuse (duloxetine), drug diversion (gabapentin and pregabalin), multiple drug overdose (pregabalin and duloxetine), overdose (duloxetine), substance abuse (gabapentin, pregabalin, and duloxetine), and substance use (gabapentin, pregabalin, and duloxetine).

Approximately 12–19% of all AERs for each drug contained one or more of the other case drug(s). When the number of reports was reduced to exclude overlap between gabapentin, pregabalin, and/or duloxetine, the numbers of unique abuse-related reports for each drug were 3435 for gabapentin, 2906 for pregabalin, and 2052 for duloxetine. For gabapentin, somnolence, drug withdrawal syndrome, and confusional state were most often co-reported with an AS-AE (Table 3). Somnolence was also the most often co-reported with a pregabalin AS-AE, while drug withdrawal syndrome had the highest co-reporting with a duloxetine AS-AE.

Based on results from the loglinear models, compared to the negative control, duloxetine, gabapentin had over six times the odds of a co-report of drug abuse (as an AS-AE) and drug withdrawal syndrome; pregabalin also had increased odds of this simultaneous report compared to duloxetine, though it was not as high as for gabapentin (Table 4). Gabapentin and pregabalin also had significantly greater odds of a co-report for an AS-AE with auditory hallucinations (OR: 4.57 and 4.28, respectively), euphoric mood (OR: 5.45 and 2.47, respectively), delusion (OR: 2.36 and 3.33, respectively), and aggression (OR: 1.98 and 2.47, respectively) compared to duloxetine. Interestingly, an abuse-specific event and drug abuser were reported together with significantly increased odds for gabapentin compared to duloxetine, but pregabalin did not have significantly increased odds. This occurred with co-reports of ataxia, psychotic disorder, and feeling abnormal, as well.

4. Discussion

This study is the first post-market pharmacovigilance study to examine gabapentin reporting in the FDA Adverse Event Reporting System and compare findings with those of a negative and a positive control. Though gabapentin, pregabalin, and duloxetine reports all produced signals for any abuse-related and abuse-specific adverse events, important differences appeared when evaluating the signals individually. Specifically, both gabapentin and pregabalin produced significant signals for ataxia, dependence, drug abuse, increased drug tolerance, and overdose. This is not surprising given that gabapentin and pregabalin have similar mechanisms of action.

Another novel aspect of the current study is that we evaluated AERs where drug abuse was indicated and assessed which effects were most often co-reported with abuse. Drug withdrawal syndrome, euphoric mood, auditory hallucinations, delusions, and aggression were more often endorsed in combination with drug abuse for gabapentin or pregabalin than for the negative control, duloxetine. While it is not necessarily remarkable that such effects have been reported for gabapentin and pregabalin (in fact several of these AEs are listed on the drugs' labels), what is particularly notable is that they were reported as occurring with drug abuse, which gives insight into the psychoactive effects that may be sought through misuse of these drugs. In a study by Schifano and colleagues (2011), data were accumulated from online anecdotes of recreational misuse of gabapentinoids and their results are concordant with those identified in this study (Schifano et al., 2011). Though pregabalin has been recognized as having abuse liability by the U.S. Drug Enforcement Administration (U.S. Department of Justice Drug Enforcement Administration Diversion Control Division, 2005)

Table 2
Frequency of abuse-related adverse event reports by case drug.2005–2015

Preferred term	Gabapentin (n = 99,977) n(%)	Pregabalin (n = 97,813) n(%)	Duloxetine (n = 73,977) n(%)
Dizziness	5251 (5.25)	6444 (6.59)	5941 (8.03)
Fall	4479 (4.48)	3599 (3.68)	2665 (3.60)
Somnolence	3326 (3.33)	5059 (5.17)	2379 (3.22)
Feeling abnormal	2859 (2.86)	3952 (4.04)	3889 (5.26)
Gait disturbance	2637 (2.64)	2934 (3.00)	1403 (1.90)
Confusional state	2476 (2.48)	2322 (2.37)	1838 (2.48)
Off-label use	2260 (2.26)	1870 (1.91)	2966 (4.01)
Overdose*	1374 (1.37)	918 (0.94)	777 (1.05)
Hallucination	958 (0.96)	886 (0.91)	790 (1.07)
Drug withdrawal syndrome	952 (0.95)	1495 (1.53)	4752 (6.42)
Disorientation	740 (0.74)	723 (0.74)	567 (0.77)
Drug abuse*	572 (0.57)	644 (0.66)	275 (0.37)
Aggression	570 (0.57)	501 (0.51)	706 (0.95)
Thinking abnormal	556 (0.56)	558 (0.57)	565 (0.76)
Intentional (drug) misuse*	551 (0.55)	540 (0.55)	427 (0.58)
Intentional overdose*	495 (0.50)	351 (0.36)	374 (0.51)
Drug dependence*	490 (0.49)	579 (0.59)	217 (0.29)
Delirium	404 (0.40)	355 (0.36)	244 (0.33)
Psychotic disorder	331 (0.33)	265 (0.27)	340 (0.46)
Mood altered	302 (0.30)	328 (0.34)	356 (0.48)
Hallucination, visual	282 (0.28)	255 (0.26)	200 (0.27)
Ataxia	249 (0.25)	224 (0.23)	100 (0.14)
Feeling drunk	230 (0.23)	587 (0.60)	168 (0.23)
Euphoric mood	185 (0.19)	538 (0.55)	151 (0.20)
Delusion	174 (0.17)	106 (0.11)	158 (0.21)
Hallucination, auditory	150 (0.15)	135 (0.14)	191 (0.26)
Incoherent	146 (0.15)	110 (0.11)	79 (0.11)
Multiple drug overdose*	146 (0.15)	39 (0.04)	49 (0.07)
Drug abuser	106 (0.11)	26 (0.03)	29 (0.04)
Drug tolerance	86 (0.09)	101 (0.10)	44 (0.06)
Dependence*	84 (0.08)	63 (0.06)	38 (0.05)
Substance abuse*	71 (0.07)	23 (0.02)	21 (0.03)
Dissociation	43 (0.04)	80 (0.08)	99 (0.13)
Hallucinations, mixed	43 (0.04)	55 (0.06)	46 (0.06)
Acute psychosis	28 (0.03)	11 (0.01)	20 (0.03)
Substance-induced psychotic disorder	26 (0.03)	10 (0.01)	11 (0.01)
Drug tolerance increased	17 (0.02)	18 (0.02)	8 (0.01)
Drug diversion*	10 (0.01)	9 (0.01)	25 (0.03)
Feeling of relaxation	8 (0.01)	26 (0.03)	18 (0.02)
Elevated mood	6 (0.01)	18 (0.02)	17 (0.02)
Substance use*	5 (0.01)	5 (0.01)	1 (0.00)
Substance abuser	2 (0.00)	0 (0.00)	0 (0.00)
Rebound psychosis	1 (0.00)	0 (0.00)	0 (0.00)
Addiction*	0 (0.00)	0 (0.00)	0 (0.00)
Drug addict	0 (0.00)	0 (0.00)	0 (0.00)
Intoxication	0 (0.00)	0 (0.00)	0 (0.00)
Prescription drug use without a prescription*	0 (0.00)	0 (0.00)	0 (0.00)
Transient psychosis	0 (0.00)	1 (0.00)	1 (0.00)
Any AR-AE	22,929 (22.93)	25,554 (26.13)	21,689 (29.32)

AR-AE: abuse-related adverse event. Note: Percentages are out of the total for each case drug. *Denotes an abuse-specific adverse event.

and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)-Europol (European Monitoring Centre for Drugs and Drug Addiction, 2012), gabapentin is still assumed by the greater prescribing community to have no abuse potential. However, the similarities between gabapentin and pregabalin in reported effects in combination with drug abuse underscore the necessity of reevaluating the abuse liability of gabapentin.

Interestingly, drug abuse was co-reported with ataxia with significantly higher odds for gabapentin than duloxetine, but the effect was not observed with pregabalin. Ataxia is a common experience of alcohol intoxication (Diener et al., 1983; Roehrs and Roth, 2001); gabapentin has produced similar effects in the human laboratory (Bisaga and Evans, 2006) and, in a study by Peterson (2009), it was identified in 137 driving impairment cases in the State of Washington. Studies to examine how gabapentin misuse may impact psychomotor effects are warranted.

Table 3
Frequency of co-reporting of an abuse-specific adverse event by case drug and non-specific-abuse-related adverse event, 2005–2015.

Preferred term	Gabapentin (n = 3435) n(%)	Pregabalin (n = 2906) n(%)	Duloxetine (n = 2052) n(%)
Somnolence	262(7.6)	269(9.3)	130(6.3)
Drug withdrawal syndrome	215(6.3)	163(5.6)	172(8.4)
Confusional state	200(5.8)	118(4.1)	104(5.1)
Fall	187(5.4)	128(4.4)	97(4.7)
Dizziness	175(5.1)	170(5.8)	140(6.8)
Feeling abnormal	144(4.2)	171(5.9)	126(6.1)
Off-label use	99(2.9)	110(3.8)	114(5.6)
Gait disturbance	86(2.5)	96(3.3)	51(2.5)
Aggression	82(2.4)	78(2.7)	46(2.2)
Hallucination	75(2.2)	53(1.8)	48(2.3)
Drug abuser	62(1.8)	13(0.4)	8(0.4)
Delirium	58(1.7)	25(0.9)	24(1.2)
Euphoric mood	54(1.6)	77(2.6)	9(0.4)
Thinking abnormal	52(1.5)	32(1.1)	29(1.4)
Disorientation	46(1.3)	37(1.3)	29(1.4)
Ataxia	45(1.3)	19(0.7)	6(0.3)
Psychotic disorder	43(1.3)	13(0.4)	20(1.0)
Drug tolerance	29(0.8)	28(1.0)	7(0.3)
Delusion	26(0.8)	19(0.7)	9(0.4)
Mood altered	26(0.8)	27(0.9)	19(0.9)
Hallucination, auditory	20(0.6)	15(0.5)	5(0.2)
Hallucination, visual	16(0.5)	14(0.5)	8(0.4)
Incoherent	16(0.5)	6(0.2)	8(0.4)
Feeling drunk	10(0.3)	18(0.6)	3(0.1)
Drug tolerance increased	9(0.3)	5(0.2)	3(0.1)
Hallucinations, mixed	4(0.1)	10(0.3)	3(0.1)
Feeling of relaxation	1(0.0)	5(0.2)	1(0.0)
Substance-induced psychotic disorder	1(0.0)	1(0.0)	0(0.0)
Substance abuser	1(0.0)	0(0.0)	0(0.0)
Dissociation	0(0.0)	1(0.0)	3(0.1)
Drug addict	0(0.0)	0(0.0)	0(0.0)
Elevated mood	0(0.0)	3(0.1)	1(0.0)
Intoxication	0(0.0)	0(0.0)	0(0.0)
Acute psychosis	0(0.0)	0(0.0)	1(0.0)
Rebound psychosis	0(0.0)	0(0.0)	0(0.0)
Transient psychosis	0(0.0)	0(0.0)	0(0.0)

Note: Frequencies and percentages exclude any cases where case drugs were co-reported.

Gabapentin abuse signals were identified using national AE reporting data from the United States. However, this is not just an American phenomenon. Our recent review (Smith et al., 2016) noted that gabapentin misuse reports have also come from the United Kingdom, Germany, Finland, India, South Africa, and France. Further, in a recent paper by Chiappini and Schifano (2016) similar methods to those used in the present study were used to examine gabapentinoid misuse in the European Medicines Agency Suspected Adverse Drug Reactions database. The authors determined that nearly 5 % of misuse/abuse/dependence spontaneous AE reports were associated with gabapentin (Chiappini and Schifano, 2016). Evaluation of the Canadian Vigilance Adverse Drug Reaction Online Database also demonstrated gabapentin misuse (Zhang and Sproule, 2015).

Though not the focus of this study, it is worth noting that the negative control, duloxetine, produced a number of significant abuse-specific signals including drug dependence, drug diversion, intentional drug misuse, and intentional drug overdose. This is particularly important because there are only a few published reports of duloxetine misuse, all of which are cases of overdose (Scanlon et al., 2016), potentially indicating an under-recognized or under-studied area.

The current study has several limitations. FAERS has a low spontaneous reporting rate, containing an average of only 6 % of all occurring drug-associated AEs (Hazell and Shakir, 2006). As a result, the incidence and prevalence of phenomena cannot be determined (de

Table 4
Loglinear odds ratio estimates for the co-occurrence of a report of an abuse-specific adverse event and a possible indicator of abuse AE by drug.

Interaction	Gabapentin OR (95% CI)	Pregabalin OR (95% CI)	Duloxetine
AS-AE * Drug withdrawal syndrome	**6.55 (5.24 - 8.19)**	**3.08 (2.44 - 3.87)**	REF
AS-AE * Euphoric mood	**5.45 (2.70 - 12.26)**	**2.47 (1.27 - 5.42)**	REF
AS-AE * Auditory hallucination	**4.57 (1.79 - 14.04)**	**4.28 (1.61 - 13.46)**	REF
AS-AE * Drug abuser	**3.01 (1.26 - 7.82)**	2.45 (0.81 - 7.78)	REF
AS-AE * Ataxia	**2.85 (1.26 - 7.68)**	1.34 (0.55 - 3.79)	REF
AS-AE * Delusion	**2.36 (1.10 - 5.49)**	**3.33 (1.48 - 8.06)**	REF
AS-AE * Drug tolerance	2.25 (0.93 - 6.06)	1.90 (0.79 - 5.10)	REF
AS-AE * Feeling drunk	2.05 (0.61 - 9.25)	1.61 (0.53 - 6.92)	REF
AS-AE * Aggression	**1.98 (1.35 - 2.92)**	**2.47 (1.68 - 3.66)**	REF
AS-AE * Psychotic disorder	**1.96 (1.14 - 3.48)**	0.77 (0.37 - 1.57)	REF
AS-AE * Feeling of relaxation	1.95 (0.07 - 54.16)	3.78 (0.54 - 76.08)	REF
AS-AE * Drug tolerance increased	1.72 (0.31 - 10.93)	0.60 (0.10 - 3.79)	REF
AS-AE * Thinking abnormal	1.52 (0.96 - 2.47)	1.03 (0.61 - 1.73)	REF
AS-AE * Mood altered	1.37 (0.75 - 2.57)	1.47 (0.80 - 2.74)	REF
AS-AE * Feeling abnormal	**1.31 (1.02 - 1.69)**	1.26 (0.99 - 1.61)	REF
AS-AE * Delirium	1.24 (0.76 - 2.10)	0.64 (0.35 - 1.16)	REF
AS-AE * Somnolence	1.24 (0.99 - 1.55)	0.91 (0.73 - 1.14)	REF
AS-AE * Confusional state	1.20 (0.94 - 1.55)	0.82 (0.62 - 1.08)	REF
AS-AE * Dizziness	1.19 (0.94 - 1.50)	1.05 (0.83 - 1.32)	REF
AS-AE * Visual hallucination	1.16 (0.50 - 2.92)	1.29 (0.54 - 3.29)	REF
AS-AE * Mixed hallucinations	1.15 (0.24 - 6.16)	2.90 (0.82 - 13.63)	REF
AS-AE * Hallucination	1.08 (0.74 - 1.58)	0.90 (0.60 - 1.36)	REF
AS-AE * Disorientation	1.02 (0.63 - 1.67)	0.93 (0.56 - 1.55)	REF
AS-AE * Fall	0.94 (0.73 - 1.22)	0.90 (0.68 - 1.19)	REF
AS-AE * Off-label use	0.93 (0.70 - 1.22)	**1.46 (1.11 - 1.92)**	REF
AS-AE * Incoherent	0.90 (0.37 - 2.32)	0.47 (0.15 - 1.41)	REF
AS-AE * Gait disturbance	0.73 (0.51 - 1.05)	0.82 (0.58 - 1.18)	REF
AS-AE * Elevated mood	–	2.98 (0.34 - 64.10)	REF
AS-AE * Dissociation	–	0.38 (0.02 - 3.01)	REF

AE: adverse event; OR: odds ratio; 95 % CI: 95 % confidence interval; AS-AE: abuse-specific adverse event; REF: referent group.
Note: Missing results correspond to occasions where no events were reported.
Boldface indicates a significant result at $p < .05$.

Boer, 2011; Rodriguez et al., 2001). However, the abuse signals detected herein provide a critical indication that further examination is required, especially in the context of a growing number of case reports of gabapentin misuse. Also, many external factors affect FAERS reporting such as the "notoriety effect" (Pariente et al., 2007), an uptick in reporting resulting from a safety alert, or the "ripple effect" where reporting is accelerated following notoriety of a drug in the same class (Pariente et al., 2007), among others (Hartnell and Wilson, 2004; Hochberg et al., 2009; Wang et al., 2010). By cumulating data over the 11-year study period, we partially mitigated the impact of fluctuations present in the data. Importantly, some of the signals detected could have been confounded by the populations for which the drugs are prescribed (e.g., gabapentinoids prescribed off-label for mood disorders) as well as due to interactions with concomitant medications. However, the purpose of this study was not to assess cause-and-effect, but rather to corroborate described effects in case reports and provide hypotheses for future controlled clinical studies. Similarly, this study did not identify the primary suspect drug for each adverse event, which could provide further elucidation on the effects experienced; this is an important area for additional investigation.

5. Conclusions

We identified abuse-related signals for gabapentin and elucidated several CNS effects that may be associated with its abuse. Future studies, including large-scale controlled pharmacological studies are needed to determine whether the CNS effects are a direct result of gabapentin. Prescribers should be aware of gabapentin's abuse liability and effects that may accompany its misuse.

Contributors

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Declaration of Competing Interest

Drs. Vickers-Smith and Sun have no competing interests to declare. Dr. Charnigo has been a co-investigator on two grants from AstraZeneca. Dr. Lofwall has no competing interests related to gabapentinoids. She has received consulting fees from CVS Caremark, Braeburn Pharmaceuticals, Titan and Indivior, research funding from Braeburn Pharmaceuticals, and honorarium from PCM Scientific (PCM Scientific has received unrestricted educational grant funding from Reckitt Benckiser Pharmaceuticals). Dr. Walsh has received consulting fees from Lilly Inc., Summit Biosciences, Otsuka Pharmaceuticals, Trevi, and World Meds over the last two years and is receiving a *gratis* drug supply from Vanda Pharmaceuticals to support an NIH-funded project. Dr. Havens has received consulting fees from Pinney Associates and unrestricted research grant funding from Purdue Pharma.

CRediT authorship contribution statement

Rachel Vickers-Smith: Conceptualization, Methodology, Writing -

original draft. **Jiangwen Sun:** Formal analysis, Writing - review & editing, Visualization. **Richard J. Charnigo:** Methodology, Writing - review & editing. **Michelle R. Lofwall:** Conceptualization, Methodology, Writing - review & editing. **Sharon L. Walsh:** Conceptualization, Methodology, Writing - review & editing. **Jennifer R.. Havens:** Conceptualization, Writing - review & editing.

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Appendix A. Supplementary data

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