HHS Public Access

Author manuscript

Addiction. Author manuscript; available in PMC 2017 August 29.

Published in final edited form as:

Addiction. 2016 July ; 111(7): 1160–1174. doi:10.1111/add.13324.

Gabapentin misuse, abuse, and diversion: A systematic review

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Abstract

Background and Aims—Since its market release, gabapentin has been presumed to have no abuse potential and subsequently has been prescribed widely off-label, despite increasing reports of gabapentin misuse. This review estimates and describes the prevalence and effects of, motivations behind, and risk factors for gabapentin misuse, abuse, and diversion.

Methods—Databases were searched for peer-reviewed articles demonstrating gabapentin misuse, characterized by taking a larger dosage than prescribed or taking gabapentin without a prescription, and diversion. All types of studies were considered; grey literature was excluded. Thirty-three articles met inclusion criteria, consisting of 23 case studies and 11 epidemiological reports. Published reports came from the USA, the UK, Germany, Finland, India, South Africa, and France, and two analyzed websites not specific to a particular country.

Results—Prevalence of gabapentin misuse in the general population was reported to be 1%, 40–65% among individuals with prescriptions, and between 15–22% within populations of people who abuse opioids. An array of subjective experiences reminiscent of opioids, benzodiazepines, and psychedelics were reported over a range of doses, including those within clinical recommendations. Gabapentin was primarily misused for recreational purposes, self-medication, or intentional self-harm and was misused alone or in combination with other substances, especially opioids, benzodiazepines, and/or alcohol. Individuals with histories of drug abuse were most often involved in its misuse.

Conclusions—Epidemiological and case report evidence suggests that the antiepileptic and analgesic medication gabapentin is being misused internationally at a rate of about 1%, with substance abuse populations at special risk for misuse/abuse.

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Competing interests:
RVS has no competing interests to declare.

Keywords

gabapentin; prescription drug misuse; systematic review; diversion; substance abuse

Introduction

Gabapentin is an analog of GABA (1); however, it does not bind to $GABA_A$ or $GABA_B$ receptors (or benzodiazepine, opioid or cannabinoid receptors), but it can increase GABA and can decrease glutamate concentrations (2, 3). Its mechanisms of antiepileptic and analgesic actions are unknown, although some have speculated, in the case of the latter, that gabapentin may reduce the release of pain-related peptides and may decrease opioid-induced hyperalgesia (4). However, a unique gabapentin binding protein has been identified (5, 6) as a subunit of the voltage-dependent calcium channel complex (7), suggesting a less specific mechanism of action through modulation of neurosignaling.

Gabapentin was approved in 1993 by the US Food and Drug Administration (FDA) initially only for treatment of epilepsy as an adjunct to anticonvulsant therapy, but in 2004 was also approved as an analgesic for post-herpetic neuralgia (8). The European Medicines Agency approved gabapentin in 2006 for epilepsy and certain types of neuropathic pain (9) and the UK National Institute for Clinical Excellence (NICE) recommends gabapentin as a first-line treatment for all neuropathic pain (10). Because its mechanism of action is unclear and it is assumed to have no abuse potential, gabapentin is widely used off-label to treat an array of disorders, including insomnia, various neuropathic pain conditions, drug and alcohol addiction, anxiety, bipolar disorder, borderline personality disorder, menopausal conditions, vertigo, pruritic disorders, and migraines. In fact, estimates of the off-label usage of gabapentin are reported to range from 83–95% of all gabapentin use (11, 12), which is estimated to account for over 90% of its sales (8). Due to illegal marketing (promoting off-label uses) of gabapentin, Pfizer was fined $420 million after it was acquired from Warner-Lambert (13).

Gabapentin is safely tolerated over a very broad range of doses from approximately 800–1800 mg/day (although package inserts suggest that patients may be treated with doses as high as 3600 mg/day). In clinical practice, dosing is typically titrated starting from lower doses (i.e., <400 mg/day) and moving rapidly upward. The European Medicines Agency (14) and the Physician Prescribing Information generally recommends dosing up to 1800 mg in adults. While substantially higher doses have been tested in clinical trials, no additional clinical benefit has been observed (15). However, other studies have examined gabapentin as acute doses in the higher dose range, and it was well tolerated. At least one imaging study has reported that gabapentin (1200 and 2400 mg) significantly (and rapidly) increased measurable concentrations of brain gamma-aminobutryric acid (GABA), one of its presumed mechanisms of action (3). Hart and colleagues (2004) examined gabapentin (600 and 1200 mg) for its potential to reduce the reinforcing effects of cocaine in the human laboratory (16). Their data reveal reductions in ratings of anxiety with both gabapentin doses (in the absence of cocaine) compared to placebo. Lile (2013) examined 600 and 1200 mg yielding significant differences from placebo on numerous outcomes, including liking, take again and

good effects (17). Bisaga and Evans (2006) examined gabapentin in combination with alcohol at acute doses of 1000 and 2000 mg (18). In this dose range, gabapentin produced some direct effect on psychomotor function but was still safely tolerated in combination with alcohol.

Despite initial views that gabapentin had no abuse potential (19–23), there have been numerous published case reports of gabapentin abuse by substance abusers in the community and penal system (24–36). The purpose of this review is to describe the international scope of gabapentin abuse (i.e., prevalence, risk factors, motivations behind misuse, how it is misused, illicit value, effects experienced) and to identify implications for practice and future research.

Methods

Definitions

The definitions presented here were used to guide article selection and are used throughout the present article to facilitate discussion. *Gabapentin* refers to the capsules, tablets, and oral solutions of which gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is the active ingredient. This definition includes the prodrug of gabapentin, gabapentin enacarbil. When discussing case reports, the dose and formulation of gabapentin will be specified, when that information is available. *Misuse* is defined as the use of a drug in a manner or for a purpose other than indicated, including, but not limited to, taking another person's medication, unprescribed or non-recommended route of administration, or a higher dosage than prescribed (37); thus, missing prescribed doses or dose reduction is not included. *Abuse* consists of persistent use of a drug despite negative consequences (37). *Dependence* refers to the physical and psychological elements associated with abuse, which include compulsion, withdrawal, and tolerance (37). *Diversion* is defined as the unauthorized selling or sharing of prescription medications, which can be either intentional (e.g., selling personal medication to someone without a prescription for that particular drug) or unintentional (e.g., theft). Diversion can occur at any point along the drug manufacturing and delivery process, however, at the core of this definition is unlawful movement of licit and regulated pharmaceuticals to the illicit marketplace (38, 39).

Search strategy and article selection

This review sought to identify peer-reviewed, published manuscripts describing cases of gabapentin misuse and/or abuse in accordance with PRISMA guidelines. The databases PubMed, Web of Science (all databases), CINAHL, PsycINFO, and Cochrane were searched utilizing terms and strategies specific to each database (Appendix 1) developed in collaboration with a qualified librarian and peer-reviewed by two additional medical librarians. All searches were conducted between May and August 2015. Only those articles written in English that described occurrences of gabapentin misuse/abuse among human populations were included. Studies describing only gabapentin toxicity, withdrawal, or dependence without misuse/abuse were excluded, as were articles describing only pregabalin misuse/abuse. Grey literature, as defined by the Institute of Medicine (40), was excluded; a well-constructed preliminary examination in Google Scholar provided over 21,000 results,

exclusion of which highlighted a vast body of evidence of gabapentin misuse. Snowball sampling (i.e., reviewing references of included papers) was then used to identify any additional articles that may have been excluded after applying index-based filters.

Data extraction was performed by the first author; all of the selected articles were reviewed by the second and third authors to assess whether they met inclusion criteria. Any disagreements regarding inclusion were discussed among all authors until agreement was reached.

Results

The initial search yielded 1,128 unique citations, of which 1,067 were excluded based on title or abstract (Figure 1). Sixty-one articles were read in their entirety to assess whether they met inclusion criteria. Twenty-eight were excluded because they did not actually describe gabapentin misuse, abuse, or diversion. The remaining 31 articles met all inclusion criteria. Snowball sampling identified 351 unique publications; 346 were excluded based on title or abstract, 2 met criteria and were included in the review. In total, this systematic review analyzed 33 articles. There were 47 case studies of gabapentin misuse/abuse found in 23 published articles from 1993 to 2015 and 11 epidemiological reports published over the same time frame (one article described both types (41)). Notably, one review article was included in this paper not due to the content of the review, but rather a statement in the introduction, which mentioned a personal communication of large-scale gabapentin abuse occurring within a drug using population in Pittsburgh, Pennsylvania (26).

The present review attempted to summarize rigorously conducted and well-presented findings on gabapentin misuse/abuse. As such, the quality of case reports could not be evaluated; therefore, this presentation focused on epidemiological and toxicological studies using case studies as secondary data. It would be detrimental to have excluded case reports, as they provide rich context from which the population data may arise. Therefore, unless clearly noted in the manuscript text that the article was a case report, the reader could assume that the study was sample-based.

Study base and data sources

The 11 epidemiological studies (all cross-sectional) selected for this analysis obtained data from unique sources (Table 1); four publications involved substance misuse/abuse populations (42–45), two examined toxicology records (41, 46), one used a population-based sample (47), two involved reports to a poison center (48, 49), and two analyzed websites with qualitative information regarding gabapentin abuse (50, 51).

Over half of the case report articles (n=14) arose from patients presenting to a hospital or general clinic with overdose or withdrawal-like symptoms (24, 25, 29, 33, 34, 36, 52–59); two came from substance abuse clinics (26, 31), three from psychiatric facilities (27, 28, 35), two from the penal system (30, 32), one from postmortem toxicology findings (60), and one from poison center reports (49).

Demographic and geographical distribution

Five epidemiology/toxicology papers provided demographic characteristics of their sample. Two toxicology studies using poison center data indicated slightly higher representation of females (60–65%) (48, 49), while another study among opioid dependent patients found no significant difference in representation by gender (51% male, p=0.58)(45). One article noted that females were significantly more likely to misuse gabapentin than males in a cohort of opioid users (percent difference=17.3%, 95% confidence interval=10.4–24.6%) (44). A toxicology paper by Peterson (2009) observed no difference in gender in the likelihood of being a positive gabapentin driving impairment case (50% male)(41). Among case studies, males had slightly higher representation than females (15 males vs. 13 females), although gender was incompletely specified in two reports (31, 49). The mean age of samples ranged between 21 and 43 in studies in which it was reported (41, 45, 46, 48, 49). The calculated mean age of case reports was 41.

Published reports came from the United States (67%, n=22), the United Kingdom (12%, n=4), Germany (3%, n=1), Finland (3%, n=1), India (3%, n=1), South Africa (3%, n=1), France (3%, n=1), and two analyzed websites not specific to a particular country (6%). While all of the articles in this review described gabapentin misuse/abuse, 12 (36%) were documented reports of overdose involving gabapentin (24, 25, 33, 48, 49, 53–57, 59, 60).

Misuse and abuse of gabapentin

Prevalence—Only one article gave an estimate of lifetime prevalence of gabapentin abuse in the general population; Kapil and colleagues (2013) surveyed a UK population-based sample of 1500 and found that 1.1% reported ever misusing gabapentin (47).

Over half of the studies described gabapentin misuse that occurred among samples with a history of or current substance misuse/abuse/dependence (n=6), the majority of which discussed opioid misuse, specifically (n=5). Smith (2012) and Baird (2013) gave reports of gabapentin misuse within Scottish populations that attended substance misuse clinics, which likely included individuals who abuse alcohol and/or drugs (42, 43). Recent cross-sectional studies of opioid abuse samples in the US and UK estimated gabapentin misuse to be between 15–22% (42, 44, 45) and gabapentin abuse with a prescription ranged from 40–65% (44, 45, 47, 49). There was little evidence of gabapentin abuse among those with a positive history of alcohol abuse or dependence. In fact, Wilens and colleagues (2015) conducted a survey among opioid dependent individuals seeking substance detoxification in the US and found no gabapentin abuse among those undergoing alcohol detoxification (45). Conversely, for opioid dependent patients, 40% reported using more gabapentin than prescribed and 13% reported using unprescribed gabapentin (45).

In Scotland in 2010, approximately 1% of all drug-related deaths were directly attributed to gabapentin (42). Further, two articles assessed toxicological results in primarily substance misusing populations; the first examined 23,479 impaired driving cases in the US and found gabapentin was involved in 0.6% of them (41), while a Finnish study reviewed 13,766 medico-legal postmortem investigations and identified gabapentin in 0.3% of the cases (46).

Doses, Cost, and Diversion—Studies indicate gabapentin is misused/abused over a wide range of doses, from within therapeutic range (900–3600 mg/day) to supratherapeutic doses. All but two articles discussed the dosage involved in gabapentin misuse (42, 47). Evidence from the US suggested that gabapentin misuse among individuals with prescriptions for gabapentin involved a higher amount than prescribed (45, 46, 61). For example, as previously mentioned, a US study found that 22% of a sample of 162 opioid-dependent patients had a prescription for gabapentin, of which 40% indicated they used more than prescribed (45). Potential explanations for this trend are tolerance and addiction as described in two clinical case discussions from France and the US, respectively (27, 36). Interestingly, according to American and European case reports, those who used gabapentin, but did not have a prescription for it, often took doses that fell within clinical guidelines, regardless of motivations behind use, though the doses were not spread out over the course of a day and it was unclear how often an individual dosed per day (31, 34).

Over half of the articles (n=7) mentioned or referred to diversion of gabapentin. Studies in the UK and US identified health services/physicians as one of the major sources of misused gabapentin, with rates ranging from 52–63% (the 63% also may include baclofen and pregabalin) (44, 47). Other sources included family or acquaintances, Internet, bought abroad (47), and drug dealers (44).

Case reports support these findings from epidemiological studies. Reports from India, the UK and US also identify family members or acquaintances as gabapentin sources. Behaviors that are markers of abuse liability, such as doctor shopping, exaggeration of symptoms, and fabrication of prescriptions, were reported in case studies from France and the US (31, 36). Due to widespread gabapentin abuse in a US correctional facility, Reccoppa and colleagues (2004) inventoried dispensed medications and found only 19 of 96 prescriptions in the possession of the inmate receiving the prescription (30).

There is a street market demand for gabapentin. An American case study stated that, “{gabapentin} tablets were sometimes sold or traded for illicit drugs” (31). In Scotland, the Drug and Crime Enforcement Agency identified the growing use of gabapentin as a cutting agent in heroin (43). In the UK and US, epidemiological studies reported the illicit market value for gabapentin ranged from <1–7 USD per pill depending on strength (42–44).

Combination with other substances—Three toxicology studies elucidated the most commonly found substances with gabapentin. The first, by Häkkinen and colleagues (2014), examined Finnish postmortem toxicological samples positive for gabapentin from 2010–2011 and found that all cases classified as gabapentin abuse also involved the use of alcohol and/or opioids (most commonly buprenorphine and tramadol) (46). Peterson (2009) conducted a study in the US, also utilizing toxicological data, which examined the presence of gabapentin in driving impairment cases. Only 7% of gabapentin-positive blood samples detected solely gabapentin; the remainder were polysubstance cases, with benzodiazepines (44%), opioids (43%), antidepressants (43%), other CNS depressants (e.g., trazodone, zolpidem; 36%), antiepileptics (25%), cannabinoids (15%), stimulants (11%), and ethanol (6%) (41). Smith and colleagues (2012) stated that postmortem toxicology reports in Scotland revealed 75% of those identifying gabapentin also included morphine and/or

methadone, which the authors said may be indicative of recent opioid dependence (43). The toxicology studies, while helpful for providing a picture of what classes of medicines were commonly found in combination with gabapentin, did not address unprescribed mixing of licit or illicit drugs.

Alternatively, several epidemiological studies did identify simultaneous combination of gabapentin with other substances for the explicit purpose of misusing them. One article discussed the misuse of gabapentin in combination with buprenorphine for the purpose of "getting high" (44). Similarly, Baird and colleagues (2014) stated that 38% of a substance misuse sample in Scotland took gabapentin (and/or pregabalin) in combination with prescribed methadone to potentiate the effects of methadone (42).

Studies in US and UK substance abuse populations, by Smith (2015) and Smith (2012) respectively, identified a greater likelihood for those misusing gabapentin to also be misusing prescription opioids (43, 44). Smith (2015) also found that individuals who reported using gabapentin to get "high" were also more likely to be misusing benzodiazepines (44), which supports the finding by Peterson (2009; discussed earlier) that benzodiazepines were the most commonly detected class of drugs in combination with gabapentin (41).

Use of gabapentin and ethanol were commonly reported together; in addition to the two toxicology studies discussed earlier (41, 46), another mentioned the misuse of gabapentin in combination with alcohol (50). An international review of recreational gabapentin misuse anecdotes described other substances that have been reported in conjunction with misused gabapentin including cannabis, SSRIs, LSD, amphetamine, and GHB (gamma-Hydroxybutyric acid) (50).

Case studies have corroborated the epidemiological findings and have also identified buprenorphine/naloxone and quetiapine as combinations of abuse with gabapentin (31, 32, 51).

Motives—A variety of motivations behind gabapentin misuse were identified, many that related to substance abuse behaviors in general, which included: recreational use (42–44, 50), control mood and/or anxiety (41), potentiate the effects of drug abuse treatment (42), and intentional self harm (49). Case reports substantiated those intentions (25, 27–35, 51, 53, 57, 59, 60), and also identified the following: pain (52), reduce cravings for/manage withdrawal from other drugs (28, 29, 35), substitute for other drugs (28, 31, 32), and addicted to gabapentin (27, 36).

Effects Experienced—Only three epidemiological studies mentioned the effects sought by misusing gabapentin (42, 43, 50); these findings were not presented as inference from a sample, rather examples accumulated from individual reporting. Six case reports also described feelings achieved from gabapentin misuse/abuse (28–32, 35). Therefore, the two types of articles were combined in this section to provide a comprehensive catalog of individual effects experienced and consequently should be interpreted with caution.

Several case studies mentioned experiencing euphoria after gabapentin misuse that was reminiscent of, but not as strong as, opioids (31, 32, 35). This feeling was achieved in combination with other drugs (e.g., buprenorphine/naloxone, methadone, baclofen, quetiapine, alcohol) (31, 32, 42, 50) as well as by using gabapentin alone (35, 43), in dosages ranging from 1500–12000 mg, though only three articles give actual amounts misused (31, 32, 35). One case study described individuals snorting gabapentin powder from capsules and experiencing a high similar to that felt after snorting cocaine (30). Another commonly reported sensation from gabapentin misuse was sedation/relaxation/calmness, which was described in six studies (28, 29, 31, 32, 43, 50). As with euphoria achieved from gabapentin misuse, sedation/relaxation/calmness was experienced in combination with other substances (e.g., quetiapine, alcohol, cannabis, buprenorphine/naloxone) (29, 31, 32) or by taking gabapentin alone (28, 50), and over a range of dosages (e.g., 600–4800 mg). Other effects experienced included: improved sociability (43, 50), marijuana-like “high” (43, 50), cocaine-like “high” (30), “amphetamine rush” (50), disassociation (50), MDMA-like “high” (50), increased energy and focus (35), improved quality of sleep (35), and becoming more talkative (50).

Discussion

Gabapentin has been presumed to have no abuse potential historically (19–23), however, this review reports evidence to the contrary. Of the 11 population-based studies and 23 case reports included here, nearly one-third report gabapentin misuse/abuse for recreational purposes and epidemiological studies from the US and UK estimate abuse rates between 40–65% just among individuals with a gabapentin prescription. Studies from the UK indicate that gabapentin has developed a prominent place as a drug of abuse; in Scottish prisons, gabapentin is among the top-requested prescription drugs of abuse (42). However, the rise in popularity of recreationally used gabapentin is occurring in the US, as well. Smith and colleagues (2015) describe a near 3000% increase in the use of gabapentin to get “high” from 2008 to 2014 among a cohort of 503 prescription drug users in the Central Appalachian region of the US (44).

Motivations for misused gabapentin can be classified largely into three basic categories: recreational (e.g., get high or substitute for more expensive drugs), self-harm, and self-medication (e.g., for pain or withdrawal symptoms from other substances). The majority of case reports involved individuals who had prescriptions for gabapentin, but took higher dosages than they were prescribed. Descriptive reports on gabapentin reveal an array of subjective experiences evocative of opioids (e.g., euphoria, talkativeness, increased energy, sedation), benzodiazepines (e.g., sedation), and psychedelics (e.g., dissociation). These effects do not appear to be specific to a particular dose and may occur well within the therapeutic range. No pattern was observed in terms of dose taken or interactions between dose and motive or dose and effects achieved, which may be partially explained by the unpredictable pharmacokinetics and non-linear bioavailability of gabapentin (62). To date, no carefully controlled human laboratory studies have been published that sought to examine and characterize the abuse potential profile of gabapentin in comparison to other prototypic drugs of abuse. Overall, further empirical research is clearly needed to better evaluate and

characterize gabapentin psychopharmacology and the risks associated with gabapentin use, especially among those using it recreationally.

It is difficult to ascertain risk factors for gabapentin misuse/abuse except history of or current drug abuse, particularly opioids, is likely one from reports available to date. While no studies to date have formally assessed a history of or current substance abuse (especially drug abuse) as a risk factor for gabapentin misuse, it was the most common characteristic detected here. This is particularly important because it indicates that the increasing trend in gabapentin abuse, notably among populations with opioid misuse, has the potential to affect an estimated 0.6–0.8% of the world's population aged 15–64 that has used opioids in the past year (63). It is important to note, however, that this review may overrepresent individuals who have abused substances, illustrating the importance of examining gabapentin misuse in the general population. Further, grey literature was excluded, which may have provided more information from which to infer risk factors for misuse, along with other characteristics of gabapentin misuse/abuse. Still, the present review emphasizes the paucity of peer-reviewed research on this important emerging topic, and provides key starting points for subsequent examination.

Gabapentin is relatively inexpensive and, in fact, many individuals can acquire it for free or a drastically reduced price under subsidy plans (64–66). Further, due to its widespread off-label prescribing worldwide (8, 11, 12), it is relatively easy to receive gabapentin by prescription, as illustrated by physicians and the health care system being the primary source of misused gabapentin in the US and UK. These factors have enabled the market to be flooded with gabapentin and it has been referred to among the drug using population as "a cheap man's high" (personal communication). It is important that prescribers recognize the current diversion of gabapentin and dispense judiciously.

Gabapentin requires a prescription, but generally has no additional controls (66–69); however, pregabalin, its close structural relative, which was approved after gabapentin, was placed into Schedule V (abuse potential) in the US (70) and included in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)-Europol annual report on new psychoactive substances of abuse (71). It was found that pregabalin had euphoric and sedative properties similar to other frequently abused substances; moreover, as it is known that tolerance and physical dependence (with withdrawal symptoms upon discontinuation) may occur in response to repeated dosing, these factors may contribute to the escalation or continued misuse of gabapentin in those abusing the drug for its psychoactive effects (72). Our review, and other non-abuse reports falling outside the scope of this study (73–79), identified that gabapentin, too, produces these effects (i.e., tolerance, physical dependence, and withdrawal) thereby warranting reevaluation of its abuse potential. However, it is important to consider in reexamination that gabapentin may be an appropriate treatment for many individuals (e.g., those in alcohol withdrawal, chronic pain, epilepsy) that may face impediments to receiving their medication upon increased control. Therefore, a risk-benefit analysis is necessary prior to any abuse potential labeling.

From published reports presented here, gabapentin is most often misused in combination with other substances, especially opioids, benzodiazepines, and alcohol, although details in

this area are sparse and necessitate systematic data collection and analysis. Concomitant use is particularly important because gabapentin is often co-prescribed with opioids, and pain patients often receive prescriptions for benzodiazepines due to anxiety and/or difficulty sleeping. Moreover, its uncontrolled status leads doctors to believe that it lacks abuse potential; thus, they may feel confident in their prescribing of gabapentin to patients with substance use histories. NHS England released advice for gabapentin prescribers that strongly recommends using it as approved, offering alternative interventions for conditions outside the licensing indications (69). Finally, benzodiazepines have been used to treat delirium resulting from gabapentin withdrawal (29) and gabapentin has been used to treat withdrawal from both benzodiazepines (80) and alcohol (19, 21). These findings suggest that these three agents may share a common neuropharmacological pathway for abuse and dependence; however, further research is necessary to explore this hypothesis.

In summary, findings from the present review suggest that gabapentin is misused/abused internationally for recreation, self-medication, or self-harm, with an array of subjective experiences. Substance abuse populations, especially individuals with a history of or current opioid misuse, appear to be at particular risk for misuse/abuse. Further studies to identify risk factors for gabapentin misuse and to characterize gabapentin's abuse liability are recommended.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Robert Shapiro for his assistance in developing the search strategy for this review.

Funding:

This work is supported by a grant awarded to JRH by the National Institute on Drug Abuse (R01DA033862). JRH has received consulting fees from Pinney Associates and unrestricted research grant funding from Purdue Pharma. SLW has received honoraria and travel reimbursement for developing and delivering educational talks through an arms-length unrestricted educational grant from Reckitt Benckiser Pharmaceuticals to PCM Scientific, UK; SLW has also received honoraria from the same grant for organizing and serving as a conference chairperson. SLW has received past salary support from a research grant from Braeburn Pharmaceuticals. SLW has received consulting fees for advising pharmaceutical companies on product development and study design, including Braeburn, Camurus, Pfizer, Novartis, Sun Pharma, Astra Zeneca and World Meds, Inc.; none of this involves gabapentinoid compounds.

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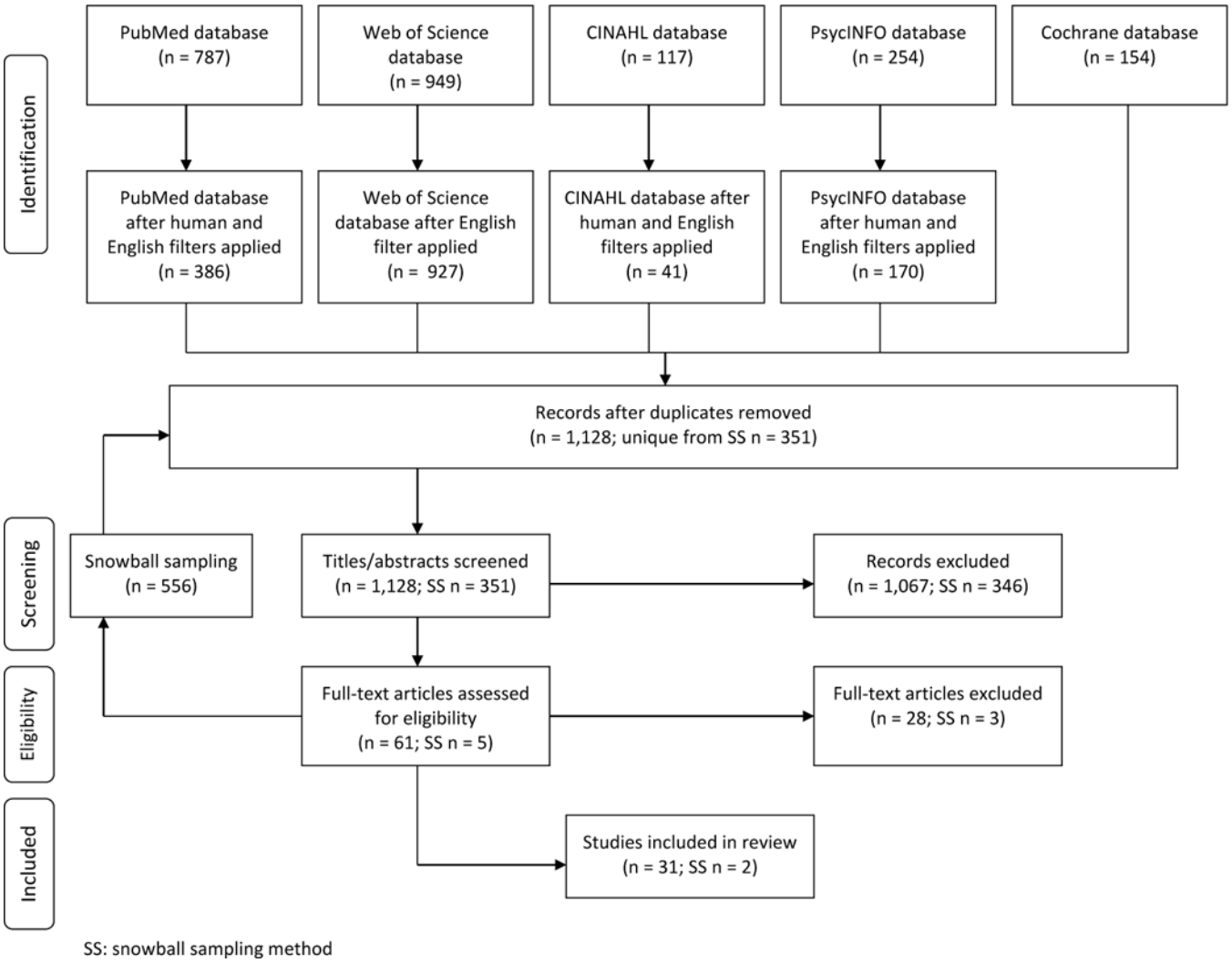

Figure 1.
Flow diagram of systematic article selection

Table 1

Summary of gabapentin misuse in reviewed articles

Study, year, and reference	Country	Type of study	Sample size and characteristics	Prevalence of gabapentin misuse/abuse	Dose	Cost, Source, Diversion	Other substances in simultaneous combination	Motives	Effects experienced	Route of administration
Baird 2013 (42)	Scotland	Paper survey	N=129 from six substance misuse clinics	19%	Not mentioned	Not mentioned	Methadone; possibly benzodiazepines	To become intoxicated, to potentiate the effects of methadone	Feeling ‘high’ or ‘stoned’	Not mentioned
Hakkinen 2014 (46)	Finland	Analysis of toxicological autopsies	N=22,421 medico-legal autopsies with toxicology samples; 8 cases of gabapentin abuse; 75.0% of gabapentin abuse cases were male; median age of gabapentin abuse cases (range): 30 (24–47)	0.31% involved in postmortem cases; 18% of those were related to drug abuse	For abuse cases, median concentration in postmortem femoral blood: 12 mg/L (range=0.62–45)	Not mentioned	Alcohol (37.5% of gabapentin abuse cases); opioids (87.5% of gabapentin abuse cases)	Not mentioned	Not mentioned	Not mentioned
Kapil 2013 (47)	UK	Online survey	N=1500 market research panel members; 49.1% male; 9.1% age 16–20, 40.5% age 21–39, 21.1% age 40–49, 29.3% age 50–59 yo	1.1% lifetime prevalence	Not mentioned	57.8% received from family or acquaintances; 47.3% from the Internet; 7.8% abroad	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Klein-Schwartz 2003 (49)	USA	Analysis of poison control cases	N=20 gabapentin exposures reported to three poison control centers; 60% female; mean age for asymptomatic cases (± SD): 21.8 ± 29.0; mean age for symptomatic cases (± SD): 23.0 ±13.9	20 of 77 gabapentin-involved cases were gabapentin-only	Mean dose (± SD) for asymptomatic cases: 1906 mg ±2238; mean dose for symptomatic cases: 6320 mg ±10926	65% involved the patient’s own medication	52 of 77 cases involved co-ingestants, but did not specify what they were and were excluded from analysis	55% was intentional suicide attempt; 5 cases of therapeutic error; 4 unintentional (general) cases	Drowsiness (x8), ataxia (x2), tachycardia (x2), dizziness (x3), hypotension (x2), nystagmus (x1), nausea/vomiting (x2), diarrhea (x1), syncope (x1), bradycardia (x1), none (x5)	Not mentioned
Peterson 2009 * (41)	USA	Analysis of blood samples	N=23,479 driving impairment cases in Washington state from 2003–2007; 50% male; mean age (± SD): 43.0 ±10.9	0.6% were positive for gabapentin	Mean concentration (±SD): 8.4 mg/L ±5.4; median: 7.0	Not mentioned	Only 9 of the gabapentin cases were positive for gabapentin only. Of the remainder, 44% also contained benzodiazepines, 43% opioids, antidepressants 43%, other CNS depressants 36%, antiepileptic drugs 25%, 15% cannabinoids, 11% stimulants, and 6% ethanol.	Not mentioned	Not mentioned	Not mentioned
Schifano 2011 (50)	Online review	Qualitative analysis of websites	N=108 websites in English, German, Spanish, Italian, Dutch, Norwegian, Finnish, and Swedish	Not mentioned	Varying doses mentioned in subjective reports ranging from 900 to 4800 mg	Mentioned online pharmacies as a source, but likely not sole source	Baclofen, cannabis, alcohol, SSRIs, LSD, ampthetamine, GHB	Not clear, but likely recreational use	Reminiscent of “amphetamine rush,” “fully sedated opiate buzz,” “disassociation like DXM,” “talkative,” “comparable to cannabis,” “buzz slightly reminiscent of MDMA”	Oral and intramuscular
Seale 2014 (51)	Online review	Brief summary of website findings	Drug forums and pharmacist blogs	Not mentioned	Not mentioned	Not mentioned	Buprenorphine/naloxone	To get “high”	Not mentioned	Not mentioned
Smith 2012 (43)	Scotland	-Qualitative reports -Prescribing data -Clinical data -Postmortem examinations	-Qualitative reports arose from from clinical experiences and a police report, unreported sample size -Prescribing data: arose from Tayside region in Scotland from 1993–2011, unreported sample size -Clinical data arose from substance misuse services in Tayside, Scotland in 2009, n=251 of those who had used	Of 251 individuals in substance misuse clinics, 5.2% receiving prescribed gabapentin; Of 1400 postmortem toxicology examinations, 48 included gabapentin, of which 36 also included methadone and/or morphine	The 5.2% receiving prescription gabapentin have a mean dose of 1343 mg	Can purchase on the street market for approximately 1 GBP per 300 mg; gabapentin is being used as a cutting agent in heroin according to a police report	Nonmedical use of prescription analgesics, morphine, methadone	Not clear, but likely recreational use	Euphoria, improved sociability, a marijuana-like ‘high’, relaxation, sense of calm, ‘zombie-like’ effects	Not mentioned

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Study, year, and reference	Country	Type of study	Sample size and characteristics	Prevalence of gabapentin misuse/abuse	Dose	Cost, Source, Diversion	Other substances in simultaneous combination	Motives	Effects experienced	Route of administration
			misuse services for 4+ years -Postmortem examinations came from Central, Tayside, and Fife Scotland in 2011, n=1400							
Smith 2015 (44)	USA	Questionnaire	N=503 nonmedical prescription opioid users from 2008 to 2014; 77.8% of gabapentin misuse cases were female	15% in past 6 months	Not mentioned	Physicians (52%) and drug dealers (36%); costs less than 1 USD per pill	Unclear if simultaneous use, but were more likely than non-gabapentin users to report past 30-day use of: immediate-release oxycodone, buprenorphine, benzodiazepines	Recreational, “to get high”	Not mentioned	Not mentioned
Wilens 2015 (45)	USA	Survey	N=162 opioid dependent patients seeking detoxification; 51% male; mean age (±SD): 33 (±10)	22% received prescription gabapentin; 40% of which reported using more than prescribed; 13% used unprescribed gabapentin; in total, 22% misused gabapentin (either more than prescribed or taking unprescribed)	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Wills 2014 (48)	USA	Medical chart review	N=347 poison center reports; 69.5% female; median age (IQR): 30 (20–44)	116 cases of gabapentin overdose	Median dose: 6000 (IQR: 2700–12000)	Not mentioned	Co-ingestion cases were excluded	Not mentioned	10% neuromuscular symptoms, 2% seizures, 41% CNS symptoms, 6% GI symptoms, 11% cardiac symptoms, 16% blood pressure, 5% metabolic signs	Not mentioned
Case Reports										
Study, year, and reference	*Country*	*Gender and age*	*History of substance abuse*	*Dose*	*Cost*	*Source/Diversion*	*Other substances in simultaneous combination*	*Motives*	*Effects experienced*	*Route of administration*
Barrueto 2002 (52)	USA	34 yo male	No	8000 mg/day	Not mentioned	Patient’s own medication	None	Manage pain	Withdrawal	Presumed oral, but not explicitly mentioned
Cantrell 2015 (24)	USA	47 yo female	Yes (D)	Up to 15.6 g once	Not mentioned	Daughter’s medication	None	Not clear	Death	Oral
Fernandez 1996 (53)	USA	32 yo male	Not mentioned	91 g once	Not mentioned	Unclear if patient’s own medication or not	Valproic acid, alcohol	Suicide	Nystagmus, slurred speech, dizziness, drowsy	Oral
Fischer 1994 (25)	USA	16 yo female	Yes (D)	48.9 g once	Not mentioned	Father’s medication	None	Self harm	Dizziness, liquid stool, lethargy, dysphoria, emotional lability	Oral
Howland 2014 (26)	USA	Not mentioned	Yes (D)	Not mentioned	Not mentioned	Mentioned street market for selling gabapentin	Opiate agents	“get high”	Not mentioned	Not mentioned
Jones 2002 (58)	USA	46 yo female	Not mentioned	2 additional doses over prescribed once	Not mentioned	Patient’s own medication	None	Not mentioned	Somnolence, hypoxia, tremulous, and hyperreflexic	Presumed oral, but not explicitly mentioned
Koschny 2014 (59)	Germany	21 yo female	Not mentioned	16 g once	Not mentioned	Not mentioned	Carvedilol, amlodipine, amitriptyline, torsemide, nicotinic acid, ketoprofen	Suicide	Cardiac failure	Oral
Kruszewski 2009 (27)	USA	38 yo male	Yes (A)	4800+ mg/day	Not mentioned	Patient’s own medication	Not clear – possibly alcohol, buspirone, bupropion	Control moods and anxiety	Delirium, addiction	Presumed oral, but not explicitly mentioned
Markowitz 1997 (28)	USA	41 yo female	Yes (D)	600–1500 mg/day	Not mentioned	Husband’s medication	None	Substitute for crack cocaine	Reduced crack cocaine cravings, relaxation	Presumed oral, but not explicitly mentioned
Middleton 2011 (60)	USA	62 yo female	No	Up to 45 g once	Not mentioned	Unclear, possibly patient’s own medication	Clonazepam	Suicide	Death	Not explicitly mentioned
Peterson ** 2009 (41)	USA	44 yo male	Not mentioned	< 2.0 mg/L	Not mentioned	Implies no medication because states the patient is “self-medicating”, but no indication of source	Quetiapine	Self medication for bipolar disorder	Lack of focus, lethargy	Presumed oral, but not explicitly mentioned.

Study, year, and reference	Country	Type of study	Sample size and characteristics	Prevalence of gabapentin misuse/abuse	Dose	Cost, Source, Diversion	Other substances in simultaneous combination	Motives	Effects experienced	Route of administration
Pittenger 2007 (29)	USA	1. 33 yo male 2. 63 yo male	1. Yes (A, D) 2.Yes (A)	1. 3600 mg/day 2. 4900 mg/day	Not mentioned for either case	Both patients used their own medication	1. Not clear – possibly cannabis, paroxetine, quetiapine 2. Not clear – possibly oxycodone	1. Control mood and withdrawals 2. Not mentioned	1. Felt calmer and reduced alcohol cravings, withdrawal 2. Withdrawal	Presumed oral for both cases, but not explicitly mentioned for either
Rasimas 2006 (54)	USA	44 yo female	Not mentioned	7 mg/L once	Not mentioned	Unclear, possibly patient's own medication	Nefazodone, possibly alcohol	Intentional self-poisoning	Tachycardia, lethargy, depressed mental status	Oral
Reccoppa*** 2004 (30)	USA	29–45 yo males	Yes (D)	300–400 mg	Not mentioned	Some misused their own medication, others misused others' prescriptions	Not clear – possibly tricyclic antidepressants, SSRIs, valproic acid, carbamazepine	"get high"	Altered mental state like snorting cocaine	Nasal insufflation
Reeves 2014 (32)	USA	38 yo male	Yes (D)	2400 mg once	Not mentioned	Not mentioned	Buprenorphine/naloxone	"get high"	Euphoria	Presumed oral, but not explicitly mentioned
Reeves 2014 (31)	USA	1. 42 yo male 2. Female 3. Unknown 4. Unknown 5. Unknown	1–2. Yes (D) 3–5. Not mentioned	1. Up to 1500 mg each dose 2. Up to 1200 mg each dose 3–5. 900–1800 mg each dose	Sold or traded for illicit drugs; specific price not mentioned	Sold or traded, or patients received their own prescription by exaggerating symptoms or false prescriptions	1. Quetiapine 2. Quetiapine and alcohol 3–5. Quetiapine	1–2. Substitute/replace cocaine 3–5. Not mentioned	1–2. Sedation and euphoria 3–5. Not mentioned	Presumed oral for all cases, but not explicitly mentioned
Roberge 2002 (33)	USA	44 yo female	Yes (D)	"handful" once	Not mentioned	Patient's own medication	Mexilitine, valproic acid, alcohol	"get high"	Slurred speech, somnolence, anisocoria, sluggishly reactive pupils, depressed gag reflex, obtundation	Oral
Rohman 2014 (34)	UK	26 yo male	Yes (D)	1600 mg once	Not mentioned	Friend	None	Recreational	Dystonia	Oral
Satish 2015 (35)	India	26 yo male	Yes (D)	400 mg – 2 g/day	Not mentioned	Initially a friend, unclear if patient eventually received own prescription	None	Recreational	Dependency, sense of well-being, increased energy, improved mood and sleep quality, increased attention span	Presumed oral, but not explicitly mentioned
Schauer 2013 (57)	USA	59 yo female	No	90 g once	Not mentioned	Patient's own medication	Hydrocodone/acetaminophen	Suicide	Nausea and mild sedation	Oral
Spiller 2002 (55)	USA	61 yo female	Not mentioned	Up to 54 g once	Not mentioned	Patient's own medication	Quetiapine	Not clear - possibly suicide	Coma, respiratory depression	Oral
Stopforth 1997 (56)	South Africa	17 yo female	Not mentioned	12 g once	Not mentioned	Not clear, but likely own patient's medication since she was epileptic	Lamotrigine	Not mentioned	Drowsy with slurred speech	Oral
Victorri-Vigneau 2007 (36)	France	67 yo female	Yes (A)	7200+ mg/day	Not mentioned	Patient's own medication	Not clear – possibly naproxen, amitriptyline	Not mentioned	Withdrawal, dependency	Presumed oral, but not explicitly mentioned

* Article is a mixed methods analysis of qualitative and quantitative data. Therefore, this article appears in both the first and second sections of this table.

** Article described 4 cases, only one of which may have been gabapentin misuse and is therefore the only incident included in summary.

*** Article combined information for 5 cases.

A = alcohol abuse; CNS = central nervous system; D = drug abuse; DXM = dextromethorphan; GBP = British pound; GHB = 4-hydroxybutanoic acid; GI = gastrointestinal; IQR = interquartile range; LSD = lysergic acid diethylamide; MDMA = 3,4-methylenedioxyamphetamine; SD = standard deviation; SSRIs = selective serotonin reuptake inhibitors; USD = United States dollar.