

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 papers 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 papers met inclusion criteria, consisting of 23 case studies and 11 epidemiological reports. Published reports came from the United States, the United Kingdom, 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 and 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 misused primarily 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 anti-epileptic and analgesic medication gabapentin is being misused internationally, with substance abuse populations at special risk for misuse/abuse.

Keywords Diversion, gabapentin, prescription drug misuse, substance abuse, systematic review.

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INTRODUCTION

Gabapentin is an analog of gamma-aminobutyric acid (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 decrease glutamate concentrations [2,3]. Its mechanisms of anti-epileptic 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 initially in 1993 by the US Food and Drug Administration (FDA) only for treatment of epilepsy as an adjunct to anti-convulsant therapy, but in 2004 was also approved as an analgesic for post-herpetic neuralgia [8]. The European Medicines Agency (EMA) 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 used widely 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 to 95% of all gabapentin use [11,12], which is estimated to account for more than 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 tolerated safely over a very broad range of doses from approximately 800 to 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 EMA [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 GABA, one of its presumed mechanisms of action [3]. Hart and colleagues [16] examined gabapentin (600 and 1200 mg) for its potential to reduce the reinforcing effects of cocaine in the human laboratory. Their data reveal reductions in ratings of anxiety with both gabapentin doses (in the absence of cocaine) compared to placebo. Lile [17] examined 600 and 1200 mg yielding significant differences from placebo on numerous outcomes, including liking, take again and good effects. Bisaga & Evans [18] examined gabapentin in combination with alcohol at acute doses of 1000 and 2000 mg. In this dose range, gabapentin produced some direct effect on psychomotor function but was still tolerated safely 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 paper selection and are used throughout the present paper 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 at 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 market-place [38,39].

Search strategy and paper selection

This review sought to identify peer-reviewed, published papers describing cases of gabapentin misuse and/or abuse in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The databases PubMed, Web of Science (all databases), CINAHL, PsycINFO and Cochrane were searched utilizing terms and strategies specific to each database (Supporting information, Appendix S1), 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 papers 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 papers 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 more than 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 papers that may have been excluded after applying index-based filters.

Data extraction was performed by the first author; all the selected papers 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 1128 unique citations, 1067 of which were excluded based on title or abstract (Fig. 1). Sixty-one papers were read in their entirety to assess whether they met inclusion criteria. Thirty were excluded because they did not actually describe gabapentin misuse, abuse or diversion. The remaining 31 papers met all inclusion criteria. Snowball sampling identified 351 unique publications; 346 were excluded based on title or abstract, two met the criteria and were included in the review. In total, this systematic review analyzed 33 papers. There were 47 case studies of gabapentin misuse/abuse found in 23 published papers from 1993 to 2015 and 11 epidemiological reports published during the same time-frame (one paper described both types [41]). Notably, one review paper 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 a rich context from which the population data may arise. Therefore, unless noted clearly in the manuscript text that the paper 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].

More than half of the case report papers ($n = 14$) 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 a 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

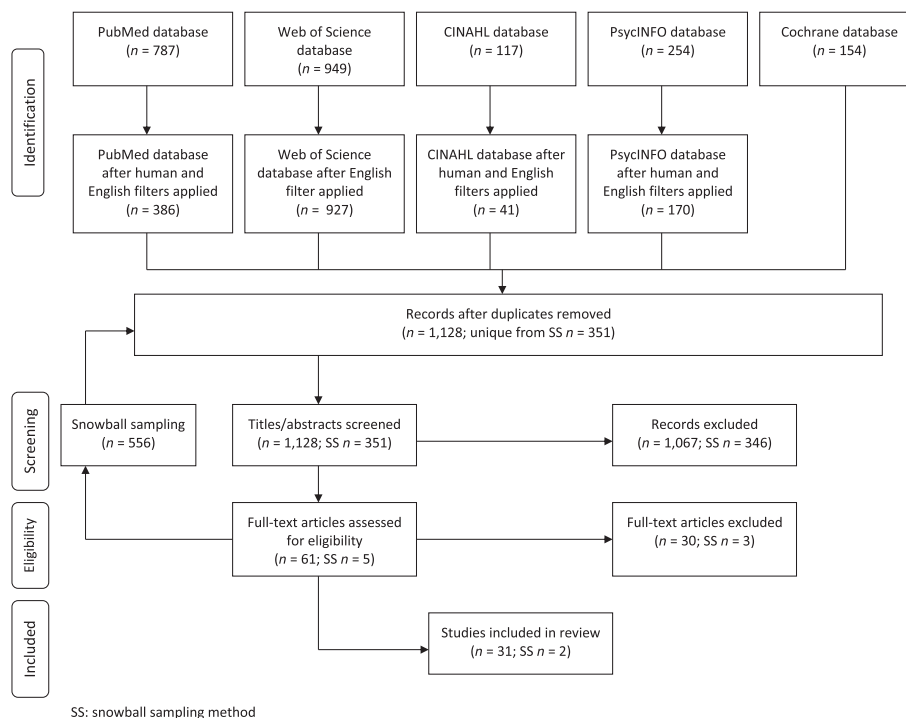


Figure 1 Flow diagram of systematic paper selection

Table 1 Summary of gabapentin misuse in reviewed paper.

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 2014 [42]	Scotland	Paper survey	$n = 129$ from six substance misuse clinics	1.9%	Not mentioned	Not mentioned	Methodone; 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	$n = 22421$ 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 years	1.1% life-time 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 (\pm SD): 21.8 \pm 29.0; mean age for symptomatic cases (\pm SD): 23.0 \pm 13.9 ($n = 23479$ driving impairment cases in	20 of 77 gabapentin-involved cases were gabapentin-only	Mean dose (\pm SD) for asymptomatic cases: 1906 mg \pm 2238; mean dose for symptomatic cases: 6320 mg \pm 10926	65% involved the patient's own medication	52 of 77 cases involved coingestants, 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 ($\times 8$), ataxia ($\times 2$), tachycardia ($\times 2$), dizziness ($\times 3$), hypotension ($\times 2$), nystagmus ($\times 1$), nausea/vomiting ($\times 2$), diarrhea ($\times 1$), syncope ($\times 1$), bradycardia ($\times 1$), none ($\times 5$)	Not mentioned
Peterson 2009 ^a [41]	USA	Analysis of blood samples	$n = 23479$ driving impairment cases in	Mean concentration	Not mentioned	Only 9 of the gabapentin	Not mentioned	Not mentioned	Not mentioned	Not mentioned

(Continues)

Schifano 2011 [50]	Online review	Qualitative analysis of websites	$n = 108$ websites in English, German, Spanish, Italian, Dutch, Norwegian, Finnish and Swedish	Not mentioned	0.6% were positive for gabapentin	(\pm SD): 8.4 mg/l \pm 5.4; median: 7.0	cases were positive for gabapentin only. Of the remainder, 44% also contained benzodiazepines, 43% opioids, 43% antidepressants	Not clear, but likely recreational use	Reminiscent of 'amphetamine rush', intramuscular 'fully sedated opiate buzz', 'disassociation like DXM', 'talkative', 'comparable to cannabis', 'buzz slightly reminiscent of MDMA'	Oral and
Seale 2014 [51]	Online review	Brief summary of website findings	Drug forums and pharmacist blogs	Not mentioned	Not mentioned	Varying doses mentioned in subjective reports ranging from 900 to 4800 mg	Mentioned online pharmacies as a source, but probably not sole source	Not clear, but likely recreational use	Not mentioned	Not mentioned
Smith 2012 [43]	Scotland	–Qualitative reports –Prescribing data –Clinical data –Postmortem examinations	–Qualitative reports arose 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,	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

(Continues)

Table 1. (Continued)

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
Smith 2015 [44]	USA	Questionnaire	<i>n</i> = 251 of those who had used misuse services for 4+ years -Postmortem examinations came from Central, Tayside, and Fife Scotland in 2011, <i>n</i> = 1400 <i>n</i> = 503 non-medical prescription opioid users from 2008 to 2014; 77.8% of gabapentin misuse cases were female	15% have misused in past 6 months	Not mentioned	Physicians (52%) and drug dealers (36%); costs less than 1 US\$ 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	<i>n</i> = 162 opioid dependent patients seeking detoxification; 51% male; mean age (\pm SD): 33 (\pm 10)	22% received prescription gabapentin; 40% of which reported using more than prescribed; 13% used unprescribed gabapentin; in total, 22% misused gabapentin (either prescribed or taking unprescribed)	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Wills 2014 [48]	USA	Medical chart review	<i>n</i> = 347 poison center reports; 69.5% female; median age (IQR): 30 (20–44)	116 cases of gabapentin overdose	Median dose: 6000 (IQR: 2700–12 000)	Not mentioned	Co-ingestion cases were excluded	Not mentioned	10% neuromuscular symptoms, 2% seizures, 41% CNS symptoms, 6% GI symptoms, 11% cardiac symptoms,	Not mentioned

(Continues)

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 years male	No	8000 mg/day	Not mentioned	Patient's own medication	None	Manage pain	16% blood pressure, 5% metabolic signs	Presumed oral, but not explicitly mentioned
Cantrell 2015 [24]	USA	47 years female	Yes (D)	Up to 15.6 g once	Not mentioned	Daughter's medication	None	Not clear	Withdrawal	Presumed oral, but not explicitly mentioned
Fernandez 1996 [53]	USA	32 years male	Not mentioned	91 g once	Not mentioned	Unclear if patient's own medication or not	Valproic acid, alcohol	Suicide	Death	Oral
Fischer 1994 [25]	USA	16 years female	Yes (D)	48.9 g once	Not mentioned	Father's medication	None	Self-harm	Nystagmus, slurred speech, dizziness, Dizziness, liquid stool, Oral	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 years female	Not mentioned	2 additional doses over prescribed once	Not mentioned	Patient's own medication	None	Not mentioned	Somnolence, hypoxia, Presumed oral, tremulous, and but not explicitly mentioned	Oral
Koschny 2014 [59]	Germany	21 years 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 years 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 years female	Yes (D)	600–1 500 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 years female	No	Up to 45 g once	Not mentioned	Unclear, possibly patient's own medication	Clonazepam	Suicide	Death	Not explicitly mentioned
Peterson ^b 2009[41]	USA	44 years male	Not mentioned	<2.0 mg/l	Not mentioned	Implies no prescription 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
Pittenger 2007 [29]	USA	1. 33 years male 2. 63 years 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	1. Control mood and withdrawals 2. Not mentioned	1. Felt calmer and reduced alcohol cravings, 2. Not mentioned	Presumed oral for both cases, but not explicitly

(Continues)

Table 1. (Continued)

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
Rasinas 2006 [54]	USA	44 years female	Not mentioned	7 mg/l once	Not mentioned	Unclear, possibly patient's own medication	2. Not clear; possibly oxycodone Nefazodone, possibly alcohol	Intentional self-poisoning	withdrawal 2. Withdrawal Tachycardia, lethargy, depressed mental status	mentioned for either Oral
Reccoppa ^c 2004 [30]	USA	29–45 years males	Yes (D)	300–400 mg	Not mentioned	Some misused their own medication, others misused others' prescriptions Not mentioned	Not clear; possibly tricyclic antidepressants, SSRIs, valproic acid, carbamazepine	'get high'	Altered mental state like snorting cocaine status	Nasal insufflation
Reeves 2014 [32]	USA	38 years 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 years 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 'Handful' once	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 years female	Yes (D)	'Handful' once	Not mentioned	Patient's own medication	Mexilitine, valproic acid, alcohol	'Get high'	Slurred speech, somnolence, anisocoria, sluggish reactive pupils, depressed gag reflex, obtundation Dystonia	Oral
Rohman 2014 [34]	UK	26 years male	Yes (D)	1600 mg once	Not mentioned	Friend	None	Recreational	Dependency, sense of well-being, improved mood and sleep quality, increased attention span	Presumed oral, but not explicitly mentioned
Satish 2015 [35]	India	26 years male	Yes (D)	400 mg to 2 g per day	Not mentioned	Initially a friend, unclear if patient eventually received own prescription	None	Recreational	Dependence, sense of well-being, improved mood and sleep quality, increased attention span	Presumed oral, but not explicitly mentioned
Schauer 2013 [57]	USA	59 years female	No	90 g once	Not mentioned	Patient's own medication	Hydrocodone/acetaminophen	Suicide	Nausea and mild sedation	Oral
Spiller 2002 [55]	USA	61 years female	Not mentioned	Up to 54 g once	Not mentioned	Patient's own medication	Quetiapine	Not clear; possibly suicide	Coma, respiratory depression	Oral

(Continues)

Stopforth 1997 [56]	South Africa	17 years 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 years 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

^aPaper is a mixed methods analysis of qualitative and quantitative data. Therefore, this paper appears in both the first and second sections of this table. ^bPaper described four cases, only one of which may have been gabapentin misuse and is therefore the only incident included in summary. ^cPaper combined information for five cases. A = alcohol abuse; CNS = central nervous system; D = drug abuse; DXAM = dextromethorphan; GBP = British pound; GHB = 4-hydroxybutanoic acid; GI = gastrointestinal; IQR = interquartile range; LSD = lysergic acid diethylamide; MDMA = 3,4-methylenedioxymphetamine; SD = standard deviation; SSRIs = selective serotonin re-uptake inhibitors; US\$ = United States dollar.

paper noted that females were significantly more likely to misuse gabapentin than males in a cohort of opioid users [percentage difference = 17.3%, 95% confidence interval (CI) = 10.4–24.6%] [44]. A toxicology paper by Peterson 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 versus 13 females), although gender was specified incompletely 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 years.

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 the papers 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 paper gave an estimate of life-time prevalence of gabapentin abuse in the general population; Kapil and colleagues surveyed a UK population-based sample of 1500 and found that 1.1% reported ever misusing gabapentin [47].

More than half 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 ($n = 5$). Baird [42] and Smith [43] gave reports of gabapentin misuse within Scottish populations that attended substance misuse clinics, which probably included individuals who abuse alcohol and/or drugs. Recent cross-sectional studies of opioid abuse samples in the United States and United Kingdom estimated gabapentin misuse to be between 15 and 22% [42,44,45] and gabapentin abuse with a prescription ranged from 40 to 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 [45] conducted a survey among opioid-dependent individuals seeking substance detoxification in the United States and found no gabapentin abuse among those undergoing alcohol detoxification. Conversely, for opioid-dependent patients, 40% reported using more gabapentin than prescribed and 13% reported using unprescribed gabapentin.

In Scotland in 2010, approximately 1% of all drug-related deaths were attributed directly to gabapentin [42]. Further, two papers assessed toxicological results in

primarily substance-misusing populations; the first examined 23, 479 impaired driving cases in the United States and found that 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 that gabapentin is misused/abused over a wide range of doses, from within therapeutic range (900–3600 mg/day) to supratherapeutic doses. All but two papers discussed the dosage involved in gabapentin misuse [42,47]. Evidence from the United States suggested that gabapentin misuse among individuals with prescriptions for gabapentin involved a higher amount than prescribed [45,46]. For example, as mentioned previously, a US study found that 22% of a sample of 162 opioid-dependent patients had a prescription for gabapentin, 40% of whom indicated that 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 United States, 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, although 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].

More than half the papers ($n = 7$) mentioned or referred to diversion of gabapentin. Studies in the United Kingdom and United States identified health services/physicians as one of the major sources of misused gabapentin, with rates ranging from 52 to 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 United Kingdom and United States also identified 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 United States [31,36]. Due to widespread gabapentin abuse in a US correctional facility, Reccoppa and colleagues [30] inventoried dispensed medications and found only 19 of 96 prescriptions in the possession of the inmate receiving the prescription.

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 United Kingdom and United States, epidemiological studies reported that the illicit market value for gabapentin ranged from less than 1 to 7 US\$ 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 [46], examined Finnish postmortem toxicological samples positive for gabapentin from 2010 to 2011 and found that all cases classified as gabapentin abuse also involved the use of alcohol and/or opioids (most commonly buprenorphine and tramadol). Peterson [41] conducted a study in the United States, 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 central nervous system (CNS) depressants (e.g. trazodone, zolpidem; 36%), anti-epileptics (25%), cannabinoids (15%), stimulants (11%) and ethanol (6%). Smith and colleagues [43] stated that postmortem toxicology reports in Scotland revealed that 75% of those identifying gabapentin also included morphine and/or methadone, which the authors said may be indicative of recent opioid dependence. 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, Baird and colleagues [42] 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. Similarly, another paper reported a greater proportion of buprenorphine misuse among recreational gabapentin users compared to those not misusing gabapentin (44 versus 26%, respectively) [44].

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

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, selective serotonin reuptake inhibitors (SSRIs), lysergic acid diethylamide (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 of mood and/or anxiety [41], potentiating 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], reduced cravings for/managed withdrawal from other drugs [28,29,35], substituted for other drugs [28,31,32] and addiction 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 as examples accumulated from individual reporting. Six case reports also described feelings achieved from gabapentin misuse/abuse [28–32,35]. Therefore, the two types of papers 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 to 12000 mg, although only three papers provide 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], 3,4-methylenedioxy-methamphetamine (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 United States and United Kingdom estimate abuse rates between 40 and 65% just among individuals with a gabapentin prescription. Studies from the United Kingdom 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 also occurring in the United States. Smith and colleagues [44] 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 United States.

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 explained partially by the unpredictable pharmacokinetics and non-linear bioavailability of gabapentin [61]. 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 prototypical drugs of abuse. Overall, further empirical research is obviously needed to evaluate and characterize gabapentin psychopharmacology and the risks associated with gabapentin use more clearly, especially among those using it recreationally.

It is difficult to ascertain risk factors for gabapentin misuse/abuse, except that history of or current drug abuse, particularly opioids, is probably one from reports available to date. While no studies yet 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 years that has used opioids in the past year [62]. It is important to note, however, that this review may over-represent 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. Nevertheless, 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 free of charge or at a drastically reduced price under subsidy plans [63–65]. Further, due to its widespread off-label prescribing world-wide [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 United States and United Kingdom. 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 [65–68]; however, pregabalin, its close structural relative, which was approved after gabapentin, was placed into Schedule V (abuse potential) in the United States [69] and included in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)-Europol annual report on new psychoactive substances of abuse [70]. 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 [71]. Our review, and other non-abuse reports falling outside the scope of this study [72–78], identified that gabapentin also produces these effects (i.e. tolerance, physical dependence and withdrawal), thereby warranting re-evaluation of its abuse potential. However, it is important to consider in re-examination that gabapentin may be an appropriate treatment for many individuals (e.g. those in alcohol withdrawal, chronic pain, epilepsy) who 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 misused most often 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. National Health Service (NHS) England released advice for gabapentin prescribers that strongly recommends using it as approved, offering alternative interventions for conditions outside the licensing indications [68]. Finally, benzodiazepines have been used to treat delirium resulting from gabapentin withdrawal [29] and gabapentin has been used to treat withdrawal from both benzodiazepines [78] 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.

Declaration of interests

R.V.S. has no competing interests to declare. J.R.H. has received consulting fees from Pinney Associates and unrestricted research grant funding from Purdue Pharma. S.L.W. 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; S.L.W. has also received honoraria from the same grant for organizing and serving as a conference chairperson. S.L.W. has received past salary support from a research grant from Braeburn Pharmaceuticals. S.L.W. 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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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Complete search strategy for each database searched from May to August 2015.