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.

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
doi. This definition includes the prodrug of gabapentin, (aminomethyl)cyclohexaneacetic acid) is the active ingredient of 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.

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Addiction
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

![Flow Diagram of Systematic Paper Selection](image-url)
<table>
<thead>
<tr>
<th>Study, year, and reference</th>
<th>Country</th>
<th>Type of study</th>
<th>Sample size and characteristics</th>
<th>Prevalence of gabapentin misuse/abuse</th>
<th>Dose</th>
<th>Cost, source, diversion</th>
<th>Other substances in simultaneous combination</th>
<th>Motives</th>
<th>Effects experienced</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baird 2014 [42]</td>
<td>Scotland</td>
<td>Paper survey</td>
<td>n = 129 from six substance misuse clinics</td>
<td>19%</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Methadone; possibly benzodiazepines</td>
<td>To become intoxicated, to potentiate the effects of methadone</td>
<td>Feeling ‘high’ or ‘stoned’</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Hakkinen 2014 [46]</td>
<td>Finland</td>
<td>Analysis of toxicological autopsies</td>
<td>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)</td>
<td>0.31% involved in postmortem cases; 18% of those were related to drug abuse</td>
<td>For abuse cases, median concentration in postmortem femoral blood: 12 mg/l (range = 0.62–45)</td>
<td>Not mentioned</td>
<td>Alcohol (37.5% of gabapentin abuse cases); opioids (87.5% of gabapentin abuse cases)</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Kapil 2013 [47]</td>
<td>UK</td>
<td>Online survey</td>
<td>n = 1500 market research panel members; 49.1% male; 9.1% age 16–20, 40.5% age 21–39, 23.1% age 40–49, 29.3% age 50–59 years</td>
<td>1.1% life-time prevalence</td>
<td>Not mentioned</td>
<td>57.8% received from family or acquaintances; 47.3% from the internet; 7.8% abroad</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Klein-Schwartz 2003 [49]</td>
<td>USA</td>
<td>Analysis of poison control cases</td>
<td>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</td>
<td>20 of 77 gabapentin-involved cases were gabapentin-only</td>
<td>Mean dose (± SD) for asymptomatic cases: 1906 mg ± 2238; mean dose for symptomatic cases: 6320 mg ± 10926</td>
<td>65% involved the patient’s own medication</td>
<td>52 of 77 cases involved coinstantants, but did not specify what they were and were excluded from analysis</td>
<td>55% was intentional suicide attempt; 5 cases of therapeutic error; 4 unintentional (general) cases</td>
<td>Drowsiness (×8), ataxia (×2), tachycardia (×2), dizziness (×3), hypotension (×2), myasthenia (×1), nausea/vomiting (×2), diarrhea (×1), syncope (×1), bradycardia (×1), none (×5)</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Peterson 2009* [41]</td>
<td>USA</td>
<td>Analysis of blood samples</td>
<td>n = 23479 driving impairment cases in</td>
<td>Mean concentration</td>
<td>Not mentioned</td>
<td>Only 9 of the gabapentin</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td></td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington state</td>
<td>2003–2007</td>
<td>50% male; mean age (± SD): 43.0 ± 10.9</td>
<td>0.6% were positive for gabapentin (± SD): 8.4 mg/l ± 5.4; median: 7.0</td>
<td>cases were positive for gabapentin only. Of the remainder, 44% also contained benzodiazepines, 43% opioids, antidepressants 43%, other CNS depressants 36%, anti-epileptic drugs 25%, 15% cannabinoids, 11% stimulants, and 6% ethanol</td>
</tr>
<tr>
<td>Schifano 2011 [50]</td>
<td>Online review</td>
<td>Qualitative analysis of websites</td>
<td>n = 108 websites in English, German, Spanish, Italian, Dutch, Norwegian, Finnish and Swedish</td>
<td>Varying doses mentioned in subjective reports ranging from 900 to 4800 mg</td>
</tr>
<tr>
<td>Seale 2014 [51]</td>
<td>Online review</td>
<td>Brief summary of website findings</td>
<td>Drug forums and pharmacist blogs</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Smith 2012 [43]</td>
<td>Scotland</td>
<td>Qualitative reports - Prescribing data - Clinical data - Postmortem examinations</td>
<td>Of 251 individuals in substance misuse clinics, 5.2% receiving prescribed gabapentin have a mean dose of 1343 mg</td>
<td>The 5.2% receiving prescription gabapentin have a mean dose of 1343 mg</td>
</tr>
</tbody>
</table>

Gabapentin misuse and diversion review (Continues)
<table>
<thead>
<tr>
<th>Study year and reference</th>
<th>Country</th>
<th>Type of study</th>
<th>Sample size and characteristics</th>
<th>Prevalence of gabapentin misuse/abuse</th>
<th>Dose</th>
<th>Cost, source, diversion</th>
<th>Other substances in simultaneous combination</th>
<th>Motives</th>
<th>Effects experienced</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith 2015 [44]</td>
<td>USA</td>
<td>Questionnaire</td>
<td>n = 503 non-medical prescription opioid users from 2008 to 2014; 77.8% of gabapentin misuse cases were female</td>
<td>15% have misused in past 6 months</td>
<td>Not mentioned</td>
<td>Physicians (52%) and drug dealers (36%); costs less than 1 US$ per pill</td>
<td>Unclear if simultaneous use, but were more likely than non-gabapentin users to report past 30-day use of immediate-release oxycodone, buprenorphine, benzodiazepines</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Wills 2014 [48]</td>
<td>USA</td>
<td>Medical chart review</td>
<td>n = 347 poison center reports; 69.5% female; median age (IQR): 30 (20–44)</td>
<td>116 cases of gabapentin overdose</td>
<td>Median dose: 6000 (IQR: 2700–12 000)</td>
<td>Not mentioned</td>
<td>Co-ingestion cases were excluded</td>
<td>Not mentioned</td>
<td>10% neuromuscular symptoms, 2% seizures, 41% CNS symptoms, 6% GI symptoms, 11% cardiac symptoms</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Wilens 2015 [45]</td>
<td>USA</td>
<td>Survey</td>
<td>n = 162 opioid dependent patients seeking detoxification; 51% male; mean age (± SD): 33 (± 10)</td>
<td>2.2% received prescription gabapentin; 40% of which reported using more than prescribed; 11% used unprescribed gabapentin; in total, 22% misused gabapentin (either more than prescribed or taking unprescribed)</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Case reports</td>
<td>Country</td>
<td>Gender and age</td>
<td>History of substance abuse</td>
<td>Dose</td>
<td>Cost</td>
<td>Source/diversion</td>
<td>Other substances in simultaneous combination</td>
<td>Motives</td>
<td>Effects experienced</td>
<td>Route of administration</td>
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<tr>
<td>Barrueto 2002 [52]</td>
<td>USA</td>
<td>34 years male</td>
<td>No</td>
<td>8000 mg/day</td>
<td>Not mentioned</td>
<td>Patient’s own medication Neither</td>
<td>None</td>
<td>Manage pain</td>
<td>Withdrawal</td>
<td>Presumed oral</td>
</tr>
<tr>
<td>Cantrell 2015 [24]</td>
<td>USA</td>
<td>47 years female</td>
<td>Yes (D)</td>
<td>Up to 15.6 g once</td>
<td>Not mentioned</td>
<td>Daughter’s medication</td>
<td>None</td>
<td>Not clear</td>
<td>Death</td>
<td>Oral</td>
</tr>
<tr>
<td>Fernandez 1996 [53]</td>
<td>USA</td>
<td>32 years male</td>
<td>Not mentioned</td>
<td>91 g once</td>
<td>Not mentioned</td>
<td>Unclear if patient’s own medication or not</td>
<td>Valproic acid, alcohol</td>
<td>Suicide</td>
<td>Nystagmus, slurred speech, dizziness, drowsy</td>
<td>Oral</td>
</tr>
<tr>
<td>Fischer 1994 [25]</td>
<td>USA</td>
<td>16 years female</td>
<td>Yes (D)</td>
<td>48.9 g once</td>
<td>Not mentioned</td>
<td>Father’s medication</td>
<td>None</td>
<td>Self-harm</td>
<td>Dizziness, liquid stool, Oral lethargy, dysphoria, emotional liability</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Howland 2014 [26]</td>
<td>USA</td>
<td>Not mentioned</td>
<td>Yes (D)</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Mentioned street market for selling gabapentin</td>
<td>None</td>
<td>'Get high'</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Jones 2002 [58]</td>
<td>USA</td>
<td>46 years female</td>
<td>Not mentioned</td>
<td>2 additional doses over prescribed once</td>
<td>Not mentioned</td>
<td>Patient’s own medication</td>
<td>None</td>
<td>Not mentioned</td>
<td>Somnolence, hypoxia</td>
<td>Presumed oral, tremulous, and hyperreflexic</td>
</tr>
<tr>
<td>Koschmy 2014 [59]</td>
<td>Germany</td>
<td>21 years female</td>
<td>Not mentioned</td>
<td>16 g once</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Curvedilol, amlodipine, amitriptyline, torsemide, nicotinic acid, ketoprofen</td>
<td>Suicide</td>
<td>Cardiac failure</td>
<td>Oral</td>
</tr>
<tr>
<td>Kruzewski 2009 [27]</td>
<td>USA</td>
<td>38 years male</td>
<td>Yes (A)</td>
<td>4800+ mg/day</td>
<td>Not mentioned</td>
<td>Patient’s own medication</td>
<td>Not clear: possibly alcohol, buspirone, bupropion</td>
<td>Control moods and anxiety</td>
<td>Delirium, addiction</td>
<td>Presumed oral, but not explicitly mentioned</td>
</tr>
<tr>
<td>Markowitz 1997 [28]</td>
<td>USA</td>
<td>41 years female</td>
<td>Yes (D)</td>
<td>600–1500 mg/day</td>
<td>Not mentioned</td>
<td>Husband’s medication</td>
<td>None</td>
<td>Substitute for crack cocaine</td>
<td>Reduced crack cocaine cravings, relaxation</td>
<td>Presumed oral, but not explicitly mentioned</td>
</tr>
<tr>
<td>Middleton 2011 [60]</td>
<td>USA</td>
<td>62 years female</td>
<td>No</td>
<td>Up to 45 g once</td>
<td>Not mentioned</td>
<td>Unclear, possibly patient’s own medication</td>
<td>Clonazepam</td>
<td>Suicide</td>
<td>Death</td>
<td>Not explicitly mentioned</td>
</tr>
<tr>
<td>Peterson 2009 [41]</td>
<td>USA</td>
<td>44 years male</td>
<td>Not mentioned</td>
<td>&lt;2.0 mg/l</td>
<td>Not mentioned</td>
<td>Implies no prescription</td>
<td>Quetiapine</td>
<td>Self-medication for bipolar disorder</td>
<td>Lack of focus, lethargy</td>
<td>Presumed oral, but not explicitly mentioned</td>
</tr>
<tr>
<td>Pittenger 2007 [29]</td>
<td>USA</td>
<td>1. 33 years male</td>
<td>1. Yes (A, D)</td>
<td>1. 3600 mg/day</td>
<td>Not mentioned</td>
<td>Both patients used their own medication</td>
<td>1. Not clear: possibly cannabis, paroxetine, quetiapine</td>
<td>1. Control mood and withdrawals</td>
<td>1. Felt calmer and reduced alcohol cravings</td>
<td>Presumed oral for both cases, but not explicitly mentioned</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. 63 years male</td>
<td>2. Yes (A)</td>
<td>2. 4900 mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

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<thead>
<tr>
<th>Study year, and reference</th>
<th>Country</th>
<th>Type of study</th>
<th>Sample size and characteristics</th>
<th>Prevalence of gabapentin misuse/abuse</th>
<th>Dose</th>
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<th>Motives</th>
<th>Effects experienced</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasimas 2006 [54]</td>
<td>USA</td>
<td>Not mentioned</td>
<td>44 years female</td>
<td>7 mg/l one</td>
<td>Not mentioned</td>
<td>Unclear; possibly patient's own medication</td>
<td>2. Not clear; possibly oxycodone</td>
<td>Withdrawal</td>
<td>'get high'</td>
<td>Oral</td>
</tr>
<tr>
<td>Nefazodone, possibly alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intentional self-poisoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reccoppa 2004 [30]</td>
<td>USA</td>
<td>Yes (D)</td>
<td>29–45 years males</td>
<td>300–400 mg</td>
<td>Not mentioned</td>
<td>Some misused their own medication</td>
<td>Not clear; possibly tricylic antidepressants, SSRIs, valproic acid, carbamazepine</td>
<td>'get high'</td>
<td>Altered mental state like snorting cocaine</td>
<td>Nasal insufflation</td>
</tr>
<tr>
<td>Reeves 2014 [32]</td>
<td>USA</td>
<td>Yes (D)</td>
<td>38 years male</td>
<td>2400 mg once</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Buprenorphine/naloxone</td>
<td>'get high'</td>
<td>Euphoria</td>
<td>Presumed oral, but not explicitly mentioned</td>
</tr>
<tr>
<td>Reeves 2014 [31]</td>
<td>USA</td>
<td>1. 42 years male</td>
<td>1–2, Yes (D) 2. Female 3. Unknown 4. Unknown 5. Unknown</td>
<td>1. Up to 1500 mg each dose 2. Up to 1200 mg each dose 3–5, 900–1800 mg each dose</td>
<td>Sold or traded for illicit drugs; specific price not mentioned</td>
<td>Sold or traded, or patients received their own prescription by exaggerating symptoms or false prescriptions</td>
<td>1. Quetiapine 2. Quetiapine and alcohol 3–5. Quetiapine</td>
<td>1–2. Substitute/replace 1–2. Sedation and euphoria 3–5. Not mentioned</td>
<td>Presumed oral for all cases, but not explicitly mentioned</td>
<td></td>
</tr>
<tr>
<td>Roberge 2002 [33]</td>
<td>USA</td>
<td>Yes (D)</td>
<td>44 years female</td>
<td>'Handful' once</td>
<td>Not mentioned</td>
<td>Patient's own medication</td>
<td>Mexilitine, valproic acid. 'Get high' alcohol</td>
<td>None</td>
<td>Sedation and euphoria</td>
<td>Oral</td>
</tr>
<tr>
<td>Rohman 2014 [34]</td>
<td>UK</td>
<td>Yes (D)</td>
<td>26 years male</td>
<td>1600 mg one</td>
<td>Not mentioned</td>
<td>Friend</td>
<td>None</td>
<td>Recreational</td>
<td>Dystoniai</td>
<td></td>
</tr>
<tr>
<td>Satish 2015 [35]</td>
<td>India</td>
<td>Yes (D)</td>
<td>26 years male</td>
<td>400 mg to 2 g per day</td>
<td>Not mentioned</td>
<td>Initially a friend, unclear if patient eventually received own prescription</td>
<td>None</td>
<td>Recreational</td>
<td>Presumed oral, but not explicitly mentioned</td>
<td></td>
</tr>
<tr>
<td>Schauer 2013 [57]</td>
<td>USA</td>
<td>No</td>
<td>59 years female</td>
<td>90 g once</td>
<td>Not mentioned</td>
<td>Patient's own medication</td>
<td>Hydrocodone/acetaminophen</td>
<td>Suicide</td>
<td>Nausea and mild sedation</td>
<td>Oral</td>
</tr>
<tr>
<td>Spiller 2002 [55]</td>
<td>USA</td>
<td>Not mentioned</td>
<td>61 years female</td>
<td>Up to 54 g once</td>
<td>Not mentioned</td>
<td>Patient's own medication</td>
<td>Quetiapine</td>
<td>Not clear: possibly suicide Coma, respiratory depression</td>
<td>Oral</td>
<td></td>
</tr>
</tbody>
</table>

(Continues)
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 medicolegal 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 buprenorphone/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. buprenorphone/naloxone, methadone, butalbital, 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, buprenorphone/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. disassociation). 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.
Gabapentin misuse and diversion review

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References


**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.