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REVIEW ARTICLE

# Current Evidence on Abuse and Misuse of Gabapentinoids

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## Abstract

This review summarizes current evidence on the abuse and misuse of the gabapentinoids pregabalin and gabapentin. Pharmacovigilance studies, register-based studies, surveys, clinical toxicology studies, and forensic toxicology studies were identified and scrutinized with the goal to define the problem, identify risk factors, and discuss possible methods to reduce the potential for abuse and misuse. Studies found that gabapentinoids are abused and misused and that individuals with a history of psychiatric disorders or substance use disorder seem to be at high risk. Moreover, some evidence supports the notion that patients with opioid use disorders may be at an increased risk of abusing gabapentinoids. Available evidence also suggests that abuse and misuse are more frequent in users of pregabalin compared with users of gabapentin. Health professionals and prescribers should be aware of the risk for misuse of pregabalin and gabapentin, which eventually could lead to abuse, substance dependence, and intoxications. Prescribing to patients belonging to risk populations such as those with psychiatric disorders or substance use disorder should be avoided if possible and, if prescribed, signs of misuse and abuse should be monitored.

**Key Points**

The gabapentinoids pregabalin and gabapentin have a potential for being abused and misused, which could result in substance dependence and intoxications.

Individuals with a history of psychiatric disorders or substance use disorder seem to be at high risk for misuse and abuse.

Some evidence suggests that patients with opioid use disorders may be at an increased risk of abusing gabapentinoids.

Available evidence suggests that abuse and misuse are more frequent in users of pregabalin compared with gabapentin.

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## 1 Introduction

The gabapentinoids, pregabalin and gabapentin, are widely used for the treatment of epileptic and pain disorders. Pregabalin is also used for generalized anxiety disorder, diabetic peripheral neuropathy, post-herpetic neuralgia, and fibromyalgia [1]. Another gabapentinoid, mirogabalin, is in clinical development and has recently been introduced in Japan for the treatment of peripheral neuropathic pain [2].

Gabapentinoids are structurally similar to gamma-aminobutyric acid (GABA); however, they do not act on GABA receptors or have effects on GABA synthesis or metabolism. They are selective ligands for the alpha-2-delta subunit of voltage-gated calcium channels (VGCC) and have been demonstrated to restrain stimulus-dependent synaptic transmitter release, mainly the excitatory transmitters glutamate and norepinephrine [3, 4]. Gabapentinoids lead to a moderate dose-dependent increase of the extracellular GABA level in the brain [3, 5], causing weak GABA-mimetic features such as relaxation and euphoria. These effects are experienced especially in the beginning of drug therapy and after use of supratherapeutic doses.

The possible risk of abuse/addiction for pregabalin was studied in vitro and in vivo during development of the substance. In a conditioned place preference test study in rats, it was found that pregabalin did not have rewarding properties and even decreased those of morphine [6]. A

later study also in rats [7] challenged these results and found that pregabalin produced the same rewarding effects under painful conditions as under pain-free conditions when given in supratherapeutic doses. In a recent study on mice [8], pregabalin produced a rewarding effect in a conditioned place preference test. In another animal study [9], mice were exposed to a partial sciatic nerve ligation or were in a control group. Both groups developed self-administration behavior indicating potential abuse liability of pregabalin. In a small study in monkeys ($n = 4$) mentioned in a review [10], self-administration of greater than ten injections a day during initial access to the drug was observed, indicating that pregabalin produced reinforcing effects.

In a review of 102 pregabalin clinical trials [11], euphoria was reported in 14 studies as an adverse effect with a prevalence between 1 and 10% (26% in one study). Patients with various diagnoses such as fibromyalgia, painful neuropathies, post-herpetic neuralgia, and generalized anxiety disorder, but also healthy volunteers were included in these studies. During the last few years, several reviews of the abuse and misuse of gabapentin and pregabalin have been published, each year adding several original publications. Our aims were to update and summarize the available evidence, describe the extent of the problem, identify risk factors, and discuss possible methods to reduce the risk for abuse and misuse.

## 2 Methods

### 2.1 Search Strategy

For this narrative literature review, PubMed was systematically searched for articles published through 31 December, 2019 utilizing the following search strategy: pregabalin OR gabapentin OR gabapentinoid AND one of the following qualifiers: abuse, misuse, overdose, or substance related disorders. In a separate search: pregabalin OR gabapentin AND forensic AND toxicology were used. Additional studies were obtained through a citation review of identified articles. JA performed the literature search.

### 2.2 Study Selection

Articles were screened for relevance through a title and abstract review. Full texts were retrieved for articles deemed relevant based on the initial assessment. Articles were considered relevant if related to gabapentinoid abuse, misuse, dependence, addiction, and overdoses in humans. Only articles written in English were considered for inclusion. Inclusion in the study was based on author consensus after a full-text review. Included studies were categorised as pharmacovigilance studies (data on reported adverse drug events), register studies (data on prescriptions, patients records), surveys (self-reported data on abuse and misuse), clinical toxicology (data on clinical intoxications), and forensic toxicology (data on post-mortem cases and from individuals driving under the influence of drugs [DUID]). Case reports and reviews were excluded as well as animal and in vitro studies. Duplicates were identified through a manual check. In total, 432 different articles were initially identified and read, 391 articles were removed and not included in the analysis. Hence, the remaining 41 articles were included and are presented in the tables.

### 2.3 Data Extraction and Assessments

To compile and describe data, details of included studies were extracted and imported to tables. JA, AKJ, and SH extracted the information from the articles. Each of the authors conducted a qualitative assessment of the identified studies and an author consensus resulted in the final tables in the publication. The information extracted from the articles were, with their definitions in parentheses: drug (the substance/s studied), time period (study period), country (the country where the data was retrieved from), study design, data source (where the data was retrieved), study population (number of individuals included in the study), and results (the outcome of the study). No study authors were contacted for additional information or clarifications of the studies included in this review.

### 2.4 Definitions of Misuse and Abuse

'Misuse' sometimes refers to all uses of illegal drugs [12]. For medicinal drugs, it may mean any types of inappropriate use, irrespective of whether there is any dependency involved, and misuse might be accidental or even unrecognized by the patient [13]. The concept of misuse in this review refers to all types of such inappropriate use. 'Abuse' on the other hand, is an active and recognized non-medical use of a substance, in most cases linked to dependence/addiction and (often) involving higher doses than normal [14]. Addiction or drug addiction is a neuropsychiatric disorder characterized by a recurring desire to continue taking the drug despite harmful consequences [15]. Although individual studies included in this review may have used slightly different definitions when discussing the results, we used the above-stated definitions.

## 3 Results

### 3.1 Clinical and Epidemiological Studies

There are several pharmacovigilance studies describing the abuse and misuse of gabapentinoids (Table 1). Two recent US studies reported data from the US Food and Drug Administration adverse event reporting system [16, 17], included pregabalin and gabapentin reports during the period 2012–16 [17] and 2005–12 [16]. Both studies, partly covering the same data, found a higher proportion of abuse-related reports for pregabalin (10.2% of 571 reports [17] and 26.1% of 97,813 reports [16]) compared with gabapentin (5.7% of 10,038 reports [17] and 22.9% of 99,977 reports [16]). A study [18] based on the data from the Eudravigilance database (spontaneously reported adverse drug reactions in the European Union) found a somewhat higher proportion of abuse-related reports for pregabalin (6.6%, of 115,616 reports) compared with gabapentin (4.8% of 90,166 reports), but the proportion of reports with a fatal outcome was more frequent in gabapentin reports compared with pregabalin reports (0.095% vs 0.023%). Concomitant use with opioids was often noted in these cases. A second study [43] (not included in Table 1) also using Eudravigilance data reported 13 cases of nasal pregabalin use in individuals with current or past substance dependency or misuse. A fatal outcome was observed in two of these cases. Three other European studies [19–21], using data from the national reporting systems, found abuse-related reports on pregabalin. The proportion of abuse-related reports was 1.5% of 521 reports in France [19], 3.5% of 15,551 reports in Germany [20], and 8.1% of 198 reports in Sweden [21].

### 3.2 Data from Drug Utilization/Prescription Databases

In recent years, a number of cohort studies concerning abuse of pregabalin and gabapentin have been published indicating that prescription of gabapentinoids as well as abuse/misuse have increased. An Australian study [22] showed that misuse-related ambulance attendances concerning pregabalin increased from 0.3 to 3.3 cases per 100,000 inhabitants from the first half of 2012 to the second half of 2017. The attendance rate was significantly correlated with prescription rates in Australia. Sedatives were often misused in combination with pregabalin (68%, 812 attendances), particularly benzodiazepines (37%, 440 attendances). A US cohort study [23] investigating 2368 drug arrests in 2016 found that 22.7% concerned gabapentin and 1.7% pregabalin. Misuse rates of gabapentin steadily increased from zero cases in 2002 to 0.03 cases per 100,000 inhabitants in 2015 according to a US survey of drug diversion [24]. In that study, gabapentin was often misused in combination with prescription opioids or with illegal opiates such as heroin.

A recent French population-based cohort study [26] found that misuse is more likely to occur in new and younger users of pregabalin. A primary addiction was developed after the first episode of drug misuse in 10.7% of pregabalin users and 11.6% of gabapentin misusers. Some studies recorded the doses taken by patients prescribed gabapentinoids. In a UK study [31], a dose above the maximum approved dose (> 600 mg/day) was observed in 1.0% of 13,480 pregabalin-treated patients. A history of substances abuse was observed in 18.4% of 136 patients compared with 14.0% of 13,480 patients in the full population. In contrast, a Swedish study reported that 8.5% of 48,550 pregabalin users were prescribed doses higher than the maximum approved dose (> 600 mg/day) [33]. Prevalence of addiction history (i.e., previous drug treatment or diagnosis for addictive disorder) in the Swedish cohort showed a wider gap between those receiving doses within the recommended maximum (20%) and those exceeding it (31%). Risk factors for being prescribed > 600 mg/day of pregabalin included sex (male), age (ages of 18–29 years vs ≥ 65 years), low income, epilepsy, previous substance use disorder treatment/diagnosis, and having previously received high doses of drugs with abuse potential. Similar figures were found in a Danish drug utilization study [32], with 9.6% and 6.5% of the 42,520-user cohort receiving > 600 mg/day for 6 and > 12 months, respectively. Male individuals and individuals prescribed antipsychotics and benzodiazepines were significantly more likely to receive doses above this recommended maximum.

A US study of insurance claim data from 2013 to 2015 [28] found that the top 1% of gabapentin users filled prescriptions for mean (median) doses of 11,274 (9534) mg/day, representing more than three times the maximum recommended dose. Intoxications, suicide, and accidents among those using gabapentinoids have also been described using drug utilization data. In Sweden, 5.2% of 191,971 individuals with at least two consecutive prescriptions for gabapentinoids were treated for suicidal behavior or died from suicide [25]. Pregabalin users had a higher risk for these outcomes compared with gabapentin users.

An Australian cohort study [27] found reports of intentional pregabalin poisonings increasing by 58% per year during the study period 2005–16. Pregabalin overdose was frequently accompanied by co-intake of opioids, benzodiazepines, and illicit drugs. Moreover, these patients had high rates of psychiatric and substance use comorbidities; 15% of pregabalin users were considered to be at high risk of misuse, and they were more likely to be younger, male, have co-prescriptions of benzodiazepines or opioids, have more individual prescribers, and higher pregabalin dosage dispensed. A UK study [29] found that pregabalin and gabapentin prescriptions increased approximately 24% per year from

**Table 1** Clinical and epidemiological studies

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Pharmacovigilance studies | | | | | | | |
| Pregabalin and gabapentin | Vickers-Smith et al., 2020 [16] | 2005–15 | USA | Post-marketing surveillance system study using pregabalin and duloxetine as controls | FDA adverse event reporting system (FAERS) | 99,977 all-cause ADEs were reported for gabapentin, 97,813 for pregabalin, and 73,977 for duloxetine | 22.9% ($n$ = 22,929) of all reports were related to abuse for gabapentin, 26.1% ($n$ = 25,554) for pregabalin: 25,554 reports and 29.3% ($n$ = 21,689) for duloxetine |
| Pregabalin and gabapentin | Evoy et al., 2019 [17] | 2012–16 | USA | Post-marketing surveillance system study | FDA adverse event reporting system (FAERS) | 571 all-cause ADEs were reported for pregabalin and 10,038 all-cause ADEs for gabapentin | 10.2% ($n$ = 58) of all reports were related to abuse for pregabalin and 5.7% ($n$ = 576) for gabapentin |
| Pregabalin and gabapentin | Chiappini and Schifano, 2016 [18] | 2004–15 | Globally | Post-marketing surveillance system study | EMA's adverse event reporting system (Eudravigilance) | 115,616 reports concerned pregabalin and 90,166 gabapentin | Proportion of all reports related to abuse:<br>Pregabalin 6.6% ($n$ = 7639 including 27 deaths)<br>Gabapentin 4.8% ($n$ = 4301 including 86 deaths) |
| Pregabalin | Bossard et al., 2016 [19] | 2010–15 | France | Post-marketing surveillance system study using clonazepam and amitriptyline as controls | French adverse event reporting system (FPVD) | Of 184,310 reports, 521 were reports on abuse or dependency | Proportion of all reports related to abuse:<br>Pregabalin 1.5% ($n$ = 8)<br>Clonazepam 3.5% ($n$ = 18)<br>Amitriptyline 0% ($n$ = 0) |
| Pregabalin | Gahr et al., 2013 [20] | 2008–12 | Germany | Post-marketing surveillance system study | German adverse event reporting system | 1552 all-cause ADRs concerned pregabalin | Proportion of all reports related to abuse:<br>pregabalin 3.5% ($n$ = 55) |
| Pregabalin | Schwan et al., 2010 [21] | 1980–2009 | Sweden | Post-marketing surveillance system study | Swedish adverse event reporting system (SWEDIS) | 82,714 all-cause ADRs were reported. Of these, 198 reports concerned abuse or addiction | Proportion of reports on abuse related to pregabalin: 8.1% ($n$ = 16) |
| Register-based studies | | | | | | | |
| Pregabalin | Crossin et al., 2019 [22] | 2012–17 | Australia | Retrospective analysis of patient records Ambulance attendance due to misuse of pregabalin | Patient records | A total of 1201 pregabalin misuse-related ambulance attendances were included | Proportion of attendances related to abuse related to pregabalin sales:<br>0.28 cases per 100,000 inhabitants during the first 6 months in 2012<br>3.32 cases per 100,000 inhabitants during the last 6 months in 2017 |

**Table 1** (continued)

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Pregabalin and gabapentin | Piper et al., 2018 [23] | 2016 | USA | Open observational cohort study | Arrests reported to Maine Diversion Aalert Program (DAP) | 2368 arrested individuals | Of 181 arrests involved non-scheduled drug, 22.7% ($n = 41$) concerned gabapentin and 1.7% ($n = 3$) pregabalin |
| Gabapentin | Buttram et al., 2017 [24] | 2002–15 | USA | Quarterly survey of prescription drug diversion reported to law enforcement by means of a brief questionnaire | Drug diversion program of the Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS) | Data from a national survey | In total, 407 cases of gabapentin diversion were reported during the period. Diversion rate: 0 during the first 2 quarters in 2002<br>0.027 per 100,000 inhabitants during the fourth quarter in 2015 |
| Pregabalin and gabapentin | Molero et al., 2019 [25] | 2006–13 | Sweden | Population-based cohort study | Prescription drug register | New users of gabapentin or pregabalin, in total 191,973 people | Treatments were associated with increased suicidal behavior or death from suicide 5.2% ($n = 10,026$), 8.9% ($n = 17,144$) had an unintentional overdose, 36.7% ($n = 70,522$) presented with head/body injuries, and 4.1% ($n = 7984$) were arrested for a violent crime Pregabalin was associated with higher hazards of all outcomes compared with gabapentin |
| Pregabalin and gabapentin | Driot et al., 2019 [26] | 2006–14 | France | Controlled cohort study | General sample of beneficiaries | New users of pregabalin (8692), gabapentin (1963), and duloxetine (3214) | Proportion of patients where misuse was considered:<br>12.8% ($n = 1112$) for pregabalin<br>6.6% ($n = 130$) for gabapentin and 9.7% ($n = 313$) for duloxetine |

**Table 1** (continued)

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Pregabalin | Cairns et al., 2019 [27] | 2012–17 | Australia | Population-based retrospective cohort study | Australian pharmaceutical benefits scheme, poison information centers, Australian toxicology service database, coronial records | 122,572 people dispensed pregabalin | Of 1158 reports of intentional poisonings, 88 pregabalin-related deaths were recorded 14.7% was considered to be at high risk of misuse according to an analysis of those prescribed pregabalin between March 2016 and February 2017 ($n$ = 58,921) |
| Gabapentin | Peckham et al., 2018 [28] | 2013–15 | USA | Cross-sectional cohort study | Commercial insurance database | 44,148 patients treated with gabapentin<br>15,335 treated with gabapentin and opioids | 2.0% ($n$ = 881) of patients with sustained overdose treated with gabapentin and no opioids<br>11.7% ($n$ = 1,789) of patients treated with gabapentin and opioids |
| Pregabalin and gabapentin | Lyndon et al., 2017 [29] | 2004–15 | UK | Multidisciplinary, register-based study | Trends in drug-related deaths and prescription data | Data on prescription and death. Pregabalin and gabapentin prescriptions increased from 1 to 10.5 million over the period | The number of deaths involving gabapentinoids increased from fewer than one per year before 2009 to 137, in 2015 79% of the deaths involved opioids<br>Death < 1/million prescriptions to 13/million prescriptions from 2009 to 2015 |
| Pregabalin | Abrahamsson et al., 2017 [30] | 2005–12 | Sweden | Retrospective register-based open cohort study | Swedish Prescribed Drug Register linked to cause of death register, and the national inpatient register | All individuals aged 18–50 years dispensed methadone or buprenorphine as maintenance treatment for opioid dependence ($n$ = 4501) heroin abusers | 22.2% had a pregabalin prescription Pregabalin was associated with overdose deaths, HR 2.82 (95% CI 1.79–4.43) |

**Table 1** (continued)

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Pregabalin | Asomaning et al., 2016 [31] | 2004–9 | UK | Observational drug utilization study of prescription data | Prescription data | In total 13,480 subjects with a prescribed pregabalin including dosing information | Proportion of patients prescribed pregabalin > 600 mg/day:<br>1% ($n = 136$)<br>Of these, 18.4% ($n = 25$) had a history of substance abuse vs 14.0% ($n = 1884$) of the entire population |
| Pregabalin | Schjerning et al., 2016 [32] | 2004–13 | Denmark | Observational drug utilization study | Drug utilization nationwide registers | 42,520 pregabalin users were identified | Proportion of patients prescribed pregabalin > 600 mg/day:<br>9.6% ($n = 4090$) for 6 months or more<br>6.5% ($n = 2765$) for 12 months or more |
| Pregabalin | Bodén et al., 2014 [33] | 2006–9 | Sweden | Prospective observational cohort study | Prescription drug register | 48,550 patients were dispensed pregabalin | Proportion of patients prescribed pregabalin > 600 mg/day:<br>8.5% ($n = 4130$) |
| Surveys | | | | | | | |
| Gabapentin | Stein et al., 2020 [34] | 2018–19 | USA | Sample of cohort of patients with opioid user disorders in withdrawal program | Survey interview | 401 of 472 patients with opioid user disorders admitted | 47% ($n = 264$) of 401 patients had used gabapentin, of them only non-prescribed gabapentin |
| Pregabalin | Al-Husseini et al., 2018 [35] | 2016–17 | Jordan | Structured interview with all customers | – | Requests for pregabalin at 14 community pharmacies in Amman, 77 customers | 45% ($n = 35$) with suspected abuse |
| Pregabalin | Al-Husseini et al., 2018 [36] | 2017 | Jordan | Semi-structured interviews | - | 11 users of pregabalin at two addiction centers | 91% ($n = 10$) of users with a previous history of substance abuse |
| Gabapentin | Vickers Smith et al., 2017 [37] | 2015 | USA | Semi-structured interview and focus group discussions | - | 33 recent users of gabapentin among non-medical users in Kentucky identified in two cohort studies | 67% ($n = 22$) reported use of prescription opioids, 15% reported use of gabapentin to get high |
| Pregabalin | Snellgrove et al., 2017 [38] | 2012–13 | Germany | Cross-sectional study Structured questionnaire and urine samples | – | 253 patients admitted to the detoxification ward for illicit drugs | 56% ($n = 142$) of patients used pregabalin, of these 92% had acquired it illegally |

**Table 1** (continued)

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Gabapentin | Bastiaens et al., 2016 [39] | NA | USA | Structured questionnaire | – | 250 patients participating in the community correctional centers treatment program | 58% ($n = 145$) with an opioid use disorder, of these 26% ($n = 37$) used gabapentin vs 4% ($n = 4$) in the remaining 105 patients |
| Pregabalin | Alblooshi et al., 2016. [40] | 2015 | UAE | Structured questionnaire | – | 250 SUD patients at the national rehabilitation center and a control group of 239 individuals from a family register | 14% ($n = 35$) of patients used pregabalin<br>The mean dose of 8.3 capsules a day, either alone or in combination with other drugs |
| Pregabalin and gabapentin | Wilens et al., 2015. [41] | 2013 | USA | Self-report questionnaire | – | 196 patients admitted to a public detoxification program: 162 opioid-dependent patients and 72 alcohol-dependent patients | Proportion of the opioid patients misused gabapentin:<br>22% ($n = 36$)<br>Proportion of the opioid patients misused pregabalin:<br>2% ($n = 3$) |
| Pregabalin and gabapentin | Baird et al., 2014. [42] | 2011–12 | Scotland | Questionnaire-based survey | – | 129 patients at 6 substance misuse clinics | 19% ($n = 25$) of the patients misused gabapentin<br>3% ($n = 4$) of the patients misused pregabalin:<br>7% ($n = 9$) were prescribed gabapentin and 1.5% ($n = 2$) pregabalin |

*ADE* adverse drug events, *ADRs* adverse drug reactions, *CI* confidence interval, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *HR* hazard rate, *NA* not available, *SUD* substance use disorder, *UAE* United Arab Emirates

**Table 2** Clinical toxicology and forensic toxicology studies

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Clinical toxicology | | | | | | | |
| Gabapentin and pregabalin | Wills et al., 2014 [44] | 2002–11 | USA | Observational retrospective study | The Toxicall database | 347 poison center cases | 33% concerned gabapentin, 7% pregabalin |
| Gabapentin and pregabalin | Daly et al., 2018 [45] | 2007–15 | Ireland | Case series | Records at 36 emergency departments | 72,391 intentional drug overdoses | 2.9% ($n = 2115$) involved gabapentinoids. These cases increased over the period: 0.5–5.5 % |
| Gabapentin | Gomes et al., 2017 [46] | 1997–2013 | Canada | Population-based nested case-control study | Various administrative databases including the Ontario Drug Benefit Database and data from the Office of the Chief Coroner of Ontario | 1256 opioid users who died, 4619 matched controls using opioids | Co-prescription of opioids and gabapentin was associated with a significantly increased odds of opioid-related death: adjusted OR 1.5, (95% CI 1.2–1.9) compared to opioid prescription alone |
| Gabapentin | Klein-Schwarz et al., 2003 [47] | 1998–2000 | USA | Prospective observational study | Reports to 3 poison centers | 20 cases of gabapentin used in doses from 50 mg to 35g | 65% ($n = 13$) had contact with a healthcare facility None were admitted for medical care |
| Pregabalin | McNamara et al., 2016 [48] | 2015 | Ireland | Cross-sectional study | Urine samples | 440 patients in opioid substitution program, 498 samples | 9.2% ($n = 39$) positive for pregabalin<br>Other drugs detected in pregabalin-positive cases were opiates 32%, benzodiazepines 80%, and cannabis 78% |
| Pregabalin | Grosshans et al., 2013 [49] | 2013 | Germany | Cohort study with control group | Urine samples | 124 patients with opiate dependency, 11 with other SUD | Among patients with opiate addiction, 12% of all specimens were positive for pregabalin vs 3% in control group |
| Gabapentin | Reynolds et al., 2019 [50] | 2013–17 | USA | Retrospectively case series | National Poison Data System | Cases reported to US poison centers 74,175 gabapentin exposures | Admission to healthcare required in 17% of isolated gabapentin exposures |
| Forensic toxicology | | | | | | | |
| Pregabalin | Lynn et al., 2020 [51] | 2013–16 | Ireland | Cohort study | National Drug-Related Deaths Index | 1489 reported poisoning deaths | Pregabalin was present in 16% ($n = 240$); 5% in 2013 to 27% in 2016 |

**Table 2** (continued)

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Pregabalin | Thompson et al., 2020 [52] | 2015–17 | Australia | Retrospective case series | Post-mortem cases where pregabalin was detected | Coronial cases | Pregabalin was identified in 5% ($n = 332$). A high rate of concurrent drug use with pregabalin was found: opioids 79% and benzodiazepines 70% |
| Gabapentin | Slavova et al., 2018 [53] | 2015 | USA | Retrospective case series | Drug overdoses from death certificates and toxicology results | 4169 drug overdose deaths in 5 US jurisdictions | Gabapentin was detected in 22% ($n = 931$) on its own and in combination with opioids in 26% ($n = 880$) |
| Pregabalin | Eastwood and Davison, 2016 [54] | 2012–14 | UK | A retrospective case series | Review of post-mortem blood concentrations in one laboratory | 70 cases positive for pregabalin | 47% ($n =339$ had a concentration higher than "reference concentration" (17 mg/L) |
| Pregabalin and gabapentin | Haukka et al., 2018 [55] | 2011–13 | Finland | Retrospective cohort study | Post-mortem cases linked to the reimbursed drug register | All cases positive for 14 prescription drugs at autopsy ($n = 2974$ cases). 786 were fatal poisonings | Proportion of pregabalin detected:<br>13% ($n = 396$) of all cases<br>29% ($n = 228$) of fatal cases<br>Proportion of gabapentin detected:<br>2% ($n = 65$) of all cases<br>3% ($n = 23$) of fatal cases |
| Pregabalin and gabapentin | Ojanperä et al., 2016 [56] | 2005, 2009, 2013 | Finland | Retrospective cohort study | Post-mortem cases related to sales calculating a fatal toxicity index | 1613 fatal intoxications | Pregabalin was involved in 2% ($n = 39$) and gabapentin in 0.4% ($n = 6$) |
| Pregabalin and gabapentin | Häkkinen et al., 2014 [57] | 2010–11 | Finland | Retrospective database study | Post-mortem blood samples | All 13,766 medicolegal deaths undergoing autopsy where toxicology was performed | Pregabalin was found in 2.3% ($n = 316$)<br>Gabapentin was found in 0.3% ($n = 43$) |
| Pregabalin | Launiainen et al., 2011 [58] | 2006–9 | Finland | Retrospective case series | Post-mortem cases | 1623 postmortem cases aged 15–34 years | Proportion of cases where pregabalin was found:<br>4.2% ($n = 68$)<br>Of which 62% ($n = 42$) were considered abuse |
| Gabapentin | Tharp et al., 2019 [59] | 2014–17 | USA | Retrospective cohort study? | Post-mortem cases and DUID cases | 104 autopsy cases and 53 DUID cases where gabapentin was found | Gabapentin contributed to death in 47% ($n = 49$)<br>Gabapentin was prescribed in 91% ($n = 39$) |

**Table 2** (continued)

| Drug | Study, year | Time period | Country | Study design | Data source | Study population | Results |
|---|---|---|---|---|---|---|---|
| Gabapentin | Peterson, 2009 [60] | 2003–7 | USA | Retrospective case series | DUID cases positive for gabapentin | 23,479 samples from individuals suspected for DUID | Proportion of cases where gabapentin was found: 0.6% ($n$ = 137)<br>Of these, 93% ($n$ = 128) also had other drugs |
| Pregabalin | Kriikku et al., 2014 [61] | 2012 | Finland | Retrospective case series | All samples from DUID suspects | 3863 samples analyzed in suspected DUID cases | Proportion of cases where pregabalin was found: 5% ($n$= 206)<br>Of these, 50% had concentrations above the therapeutic interval |

*CI* confidence interval, *DUID* driving under the influence of drugs, *OR* odds ratio, *SUD* substance use disorder

1 million in 2004 to 10.5 million in 2015. Gabapentin deaths also increased during the same period from < 1 in 2009 to 137 in 2015. Opioids were involved in 79% of these deaths.

## 3.3 Indications of Abuse/Non-Medical Use in Surveys/Questionnaires

During recent years, a numbers of surveys have been conducted among users of gabapentinoids in countries such as USA [37, 39, 41], Germany [38], Scotland [42], Jordan [35, 36], and United Arab Emirates [40]. In a US study [37], 33 individuals self-reported recent non-medical gabapentin use. Their regular gabapentin use began often >10 years prior, typically prescribed for a legitimate medical reason (e.g., pain, anxiety, opioid detoxification), albeit often off-label. Participants took gabapentin with other drugs including buprenorphine, opioids, cocaine, and caffeine to produce desired effects such as muscle relaxation, pain reduction, sleep, sensation of drunkenness, and euphoria.

At the Center for Psychiatry in Southern Germany [38], 253 out of 281 patients on a detoxification ward for illicit drugs self-reported using pregabalin at least once and 92% admitted to obtaining at least some of it from illegal sources. Reasons for pregabalin use included opioid withdrawal symptoms, augmentation of other substances' psychotropic effects, and to experience the effects of pregabalin itself. Predictors for pregabalin use were opioid and sedative use as well as younger age.

In the second US study [39], 250 former inmates with substance use disorders living in a correctional community center responded to a questionnaire. Prescription drug misuse was reported in 62% of the patients and 16% reported misuse of gabapentin in the past. A significantly higher proportion of patients with an opioid use disorder (26%) endorsed gabapentin abuse compared with 4% of those without an opioid use disorder.

In another study [42], a questionnaire-based survey was carried out in six substance misuse clinics in Scotland. Among the 129 patients recruited, 8% reported that they were prescribed gabapentinoids and 22% admitted that they were abusing gabapentinoids and of these, 38% abused gabapentinoids to potentiate euphoria experienced from methadone.

## 3.4 Gabapentinoids and Toxicology: Clinical and Forensic

### 3.4.1 Clinical Toxicology

Clinical and forensic toxicological studies are summarized in Table 2. A study from Ireland [45] showed that gabapentinoids were involved in 2.9% of the 72,391 intentional drug overdoses recorded at emergency departments. These

intentional drug overdoses increased from 0.5% in 2007 to 5.5% in 2015. In a study of opioid-related deaths [46], co-prescription of opioids and gabapentin was significantly associated with opioid-related death relative to opioid prescription alone. Moreover, moderate- and high-dose gabapentin use was associated with an increased risk for opioid-related death. In a study of 347 cases of overdoses of newer anticonvulsants identified in US poison center records, 33% concerned gabapentin and 7% pregabalin [44]. Most of the cases where pregabalin and gabapentin were implicated had minor or moderate clinical effects, which is in agreement with a previous study of patients intoxicated with gabapentin [47].

#### 3.4.2 Forensic Toxicology

The prevalence of gabapentinoids in forensic settings has been evaluated in a number of studies (Table 2) with a focus on abuse and toxicity. Most of these studies were based on post-mortem data but some were generated by data from suspected DUID cases.

An Irish study found an increase in pregabalin-positive poisoning deaths from 5% of all cases in 2013 to 26% in 2016 [51]. The odds of being pregabalin positive increased with female sex, opioid misuse, recent treatment for problem drug use, and the year of death. In a study of 104 forensic autopsy cases in the USA where gabapentin had been detected post-mortem, gabapentin was considered to be directly involved in the death in nearly half of the cases (47%) [59]. The drug was prescribed legitimately to 91% of the individuals whose death was gabapentin related, and 84% had a known history of prescription drug abuse or misuse. In another study, 4.4% of coronial cases in Australia between 2015 and 2017 were found positive for pregabalin [52]. In a majority of these cases (58%), the cause of death was drug related and in 40% a mixed drug toxicity was described. Concurrent drug use was common and opioids were identified in 79% of all positive cases. Benzodiazepines and antidepressant drugs were also frequent findings. During 2015, gabapentin was found in 22% of all drug overdose deaths, and 26% of those positive for opioids, in five US jurisdictions 53].

In a series of 93 fatalities from the UK, where pregabalin was found and considered the cause of death or contributory to death, other drugs were present in all cases; antidepressant drugs were found in more than 90% of the cases and opioids in 65% of the cases [62]. In 30 US post-mortem cases where gabapentin was found at autopsy [63], mixed-drug toxicity was determined in 47% of the cases.

Four Finnish studies have been published on the subject of this article (see Table 2). Haukka et al. [55] published a study where pregabalin was found in 396 and gabapentin in 65 of all forensically investigated deaths during 2011–13. For pregabalin, 228 cases were fatal poisonings and for gabapentin, 23 were fatal poisonings. For pregabalin, 139 of all cases and for gabapentin 12 of all cases were considered as non-medical use (no prescription within 365 days). Among the cases who died from fatal poisonings, 45% had non-medical use for pregabalin and 30% for gabapentin. In another Finnish study [57], pregabalin was found in 2.3% of all cases subject to forensic toxicology and for gabapentin, the corresponding proportion was 0.3%. Drug abuse was associated with 48% and 19% of pregabalin and gabapentin cases, respectively. Pregabalin poisoning accounted for 10% of all pregabalin cases and gabapentin poisoning for 5% of all gabapentin cases. In the drug abuser cases, pregabalin poisoning represented 19%, and gabapentin poisoning 12%. Concomitant opioid use was noted in 91% in the pregabalin abuser group and in 88% in the gabapentin abuser group.

Three studies focused on DUID cases. The recent US study mentioned above [59] also investigated 53 non-fatal cases of motor vehicle drivers suspected of DUID. In another US study [60], 137 DUID cases were identified whose samples were positive for gabapentin submitted to the Washington State Toxicology Laboratory between 2003 and 2007. The concentrations of gabapentin in blood from DUID cases had a range of < 2.0–24.7 mg/L with a mean of 8.4 ± 5.4 mg/L and a median of 7.0 mg/L. Of the cases studied, only 7% were positive for gabapentin alone. In Finland [61], pregabalin was detected in 5% of 3863 cases of DUID suspects in 2012. Serum concentration was above the therapeutic range in nearly 50% of the cases and other drugs were found in most cases.

## 4 Discussion

Mounting evidence shows that gabapentinoids are abused and misused and that individuals with a history of abuse are at an increased risk. In a previous review, Smith et al. [64] estimated the prevalence of gabapentin abuse and misuse to be 40–65% among individuals with prescriptions and 15–22% in populations abusing opioids compared with 1% in the general population. A lifetime prevalence of misuse of 1.1% for gabapentin and 0.5% for pregabalin was also observed in a UK online survey [65] performed by a global market research company. In pharmacovigilance studies based on spontaneous reports of adverse events for pregabalin and gabapentin, 1.5–10% of reports were classified as misuse, abuse, and/or dependence (Table 1). Abuse and misuse of gabapentinoids seem to have increased in recent years. In the study by Chiappini and Schifano [18], 7639 reports concerning misuse, abuse, or dependence for pregabalin and 4301 for gabapentin were identified using Eudravigilance data for the period 2004–15. More than 75% of all reports were reported after 2012.

### 4.1 Risk Populations

Available evidence shows that gabapentinoid abuse is more prevalent among patients with substance use disorders, in particular opioid abuse. There are studies reporting that 15–22% and 3–68% of patients with opioid use disorders abuse gabapentin and pregabalin, respectively [39–42, 48, 49, 64]. Although the studies are undertaken in different countries using different methodologies, they support the same general picture. In a study of patients treated for opioid addiction in a substance use disorder clinic in USA [41], 22% misused gabapentin and 7% misused pregabalin. That contrasts with those treated for non-opioid addiction where no one misused gabapentinoids. The same pattern was observed in a German study [49]. Patients treated for opioid addiction abused pregabalin in 12% of the cases, whereas those treated for non-opioid addiction abused pregabalin in only 2% of the cases. In Italian patients with a history of opiate dependency and in methadone treatment programs where pregabalin was detected in 14% of hair samples, 57% of those patients also used other drugs [66]. Among former US inmates, opioid abusers were significantly more likely to misuse gabapentin than those with a non-opioid substance use disorder, 26% vs 4% [39]. Other studies confirm high rates of gabapentinoid abuse in opioid addicts [20, 21, 42, 64, 66–68]. One study [40] reported that more than 60% of opioid addicts misused gabapentinoids. A survey among opioid abusers found that on average gabapentin was used recreationally in 25 of the last 30 days [64]. Among 401 participants with opioid use disorder recruited from a managed withdrawal program in the USA, 66% had used gabapentin [34]. Of these, 20% had used only prescribed gabapentin, while 32% had used both prescribed and non-prescribed gabapentin. Moreover, earlier abuse of cocaine has also been mentioned as a risk factor for gabapentinoid abuse [48, 69].

Different reasons why abuse of gabapentinoids is higher among opioid abusers have been proposed. It has been suggested that they might relieve opioid withdrawal syndromes or treat uncontrolled pain [39, 49]. Another suggested explanation is that with reduced prescribing of opioids and benzodiazepines, patients are substituting other licit or illicit drugs because of the greater availability [66, 70]. In a small interview study among opioid users, augmenting the opioid high was a common reason for combining a variety of substances with opioids [71]. It has been reported that patients undergoing substance use disorder treatment use gabapentinoid to potentiate the effects of methadone or buprenorphine, as well as to avoid detection during urine monitoring [34, 39, 42, 49, 72]. In one study [34], the most common reasons for intake among those using non-prescribed gabapentin or using both prescribed and diverted gabapentin were to get high, increase the effects of heroin, substitute for opioids, and aid with opioid withdrawal. It has also been suggested that opioid-tolerant patients might desire the euphoric effects of new drugs such as the gabapentinoids.

Abuse of gabapentinoids typically involves supratherapeutic doses (i.e., pregabalin > 600 mg and gabapentin > 3600 mg). Tachyphylaxis has been reported to develop rapidly and repeat abusers may therefore continue to increase the dose [73]. National drug utilization data have confirmed that many patients receive doses higher than recommended; this includes, for example, 8.5% and 9.6% of the patients prescribed pregabalin in Sweden [32] and Denmark [33], respectively. Analysis of pregabalin abuse/dependence adverse events in Germany revealed mean daily doses of 1424 mg and a case series of recreational pregabalin abuse documented doses of 500–1400 mg [20]. In different case reports, doses varied from 800 to 7500 mg and gabapentin doses between 1500 and 12,000 mg [69, 72, 74–77].

### 4.2 Abuse Potential for Pregabalin and Gabapentin

Available evidence suggests that pregabalin is the preferred gabapentinoid possibly owing to pharmacological differences between the two substances [1, 3]. Pregabalin is absorbed more rapidly (maximum concentration within 1.5 hours) after oral intake and it has a higher bioavailability compared with gabapentin (>90% vs 33–66 %) creating a faster onset of euphoria [1, 3, 78]. Moreover, gabapentin seems to have a dose-dependent absorption, giving a non-linear dose-blood concentration relationship (at higher doses) [1, 3, 78]. Pregabalin is also stated to have a stronger inhibitory action on the α2δ-subunit-containing VGCC compared with gabapentin [1, 3].

There are a few studies where the abuse potential has been compared between the two substances. Overall, the abuse potential was shown to be higher for pregabalin than gabapentin based on adverse drug reporting data from the USA [17] and Europe [18]. Apart from pharmacovigilance and drug register studies and other systematic studies, there are several case presentations related to the abuse of gabapentinoids. These reports indicate that the dependence on pregabalin might be stronger and more sustaining than on gabapentin [78].

We have only found one study on the human abuse potential of the new gabapentinoid mirogabalin [79]. That study reported that supratherapeutic-dose mirogabalin was better liked by recreational polydrug users than users of placebo. However, there is no information available on the abuse potential of mirogabalin compared with pregabalin and/or gabapentin.

### 4.3 Clinical Effects and Biological Mechanisms

A meta-analysis of 38 clinical trials showed that euphoria was the second, most commonly reported adverse event

for pregabalin [80], typically reported in individuals using higher pregabalin doses. Supratherapeutic doses may produce sedation, dissociation, relaxation, contentment, uninhibited behavior, improved sociability, empathy, and hallucinations [68, 72, 77]. Euphoria has also been reported to be significantly more common among pregabalin users than those treated with placebo [81]. Interestingly, early treatment response was improved in those who experienced euphoria. Somewhat different results were seen in a study by Zacny et al. [70] showing that abuse liability-related subjective effects such as drug liking and desire to take the drug again were not increased by pregabalin dose. Moreover, psychomotor performance was not affected by pregabalin use.

Several addictive drugs have in common that they increase the extracellular dopaminergic activity in the mesolimbic reward system [82–84]. This has however not been shown for gabapentinoids. A microdialysis study in rats found that gabapentin produced a modest increase in extracellular nucleus accumbens GABA levels but failed to alter either the basal or cocaine-enhanced dopamine activity in this key region of the reward system [5]. There have been speculations that there might be a different range of neurotransmitter involvement and receptor activation in high/very high pregabalin doses [85]. Pregabalin is a known inhibitor of the α2δ-subunit-containing VGCC. These VGCCs are located predominantly in presynaptic membranes and it has been demonstrated that gabapentinoids restrain stimulus-dependent synaptic transmitter release, mainly the excitatory transmitters glutamate and norepinephrine, but not dopamine [3, 4, 86]. Gabapentinoids might thereby act against aberrant neuronal over-excitation [87, 88]. Therapeutic doses of gabapentinoids are dose-dependently associated with a modest increase of the extracellular GABA concentration in brain tissue [1, 3, 5, 89], i.e., they have weak GABA mimetic features that might drive the relaxation and euphoria experienced in the beginning of drug therapy and during an overdose. For pregabalin, conditioned place preference test studies in rats indicated that only high intraperitoneal (but not oral) doses had an effect that could be interpreted as an ability to develop addiction [7]. It has been suggested that gabapentinoids may induce a subjective feeling of "liking" (euphoric high) owing to their GABA-mimetic action, but limited levels of behavioral dependence related to "wanting" [78].

A possible mechanism behind the fact that gabapentinoids often are combined with opioids has been suggested by Vashchinkina et al. [90]. Using a mice model, they found that pregabalin counteracted both the reinforcing and withdrawal effects of opioids. In addition, they also reported a potentiating effect of pregabalin on neuroplasticity leading to an increased conditioned place preference.

### 4.4 Sources of the Drugs

In a study from the UK [65], it was found that misused gabapentinoids most often are obtained from healthcare providers (63%). Thus, many are prescribed the drugs but misuse it recreationally. The same pattern was seen in a US study [41]. Opioid-dependent patients admitted misuse in 50% of cases of those prescribed pregabalin and in 40% of those prescribed gabapentin. Patients not prescribed a gabapentinoid admitted misuse of pregabalin in 6% of cases and gabapentin in 13% of cases. However, gabapentinoids are also readily available from drug dealers or the Internet [21, 49, 73]. To minimize cravings or continue to get 'highs' in the setting of mandatory urine controls or in a lack of other drugs of abuse [40, 42, 49, 72, 75], gabapentinoid abuse might be initiated to replace for example, cocaine or opioids [75, 91].

In general, there has been a notable increase in prescribing of gabapentinoids during the last 15 years. In a US adult population, the prevalence of gabapentin prescribing increased nearly two-fold from 2009 to 2016 [92]. Essentially, the same pattern was seen in a study of the use of gabapentinoid medications among US adults with cancer over the period 2005–15 [93] and in a UK study investigating prescribing trends of gabapentin and pregabalin over the years 2013–15 [94].

According to a recent US study using data from the National Ambulatory Medical Care Survey, a four-fold increase in annual gabapentinoid-involved visits was observed from 2003 to 2016 [95]. Concomitant use with other drugs such as opioids (32.9%) or benzodiazepines (15.3%) was frequent in these cases. Most of the gabapentinoids were prescribed by a primary care physician (45.8%) and only few by a psychiatrist (4.8%). However, it was noted that most (96.6%) of the gabapentinoid visits did not have an approved indication for the gabapentinoids among the first three recorded diagnoses. The increase in gabapentinoid medication in the USA in recent years has been confirmed by other studies [92, 93]. The reason for the seemingly higher prevalence of prescription drug misuse/abuse of the gabapentinoids in the USA compared with European countries could at least partly be explained by differences in the prescriber's perception of the safety of gabapentinoids.

Prescribers in the USA, in contrast to European prescribers, might consider gabapentinoids a safer non-opioid pain medication in the context of the opioid overdose epidemic in the USA [92, 96]. However, other differences in regulations, healthcare systems, ease of access, and perceptions by users might also add to these differences. However, the problem with the misuse of gabapentinoids was also reported

as common in the UK, where a majority of gabapentinoid prescriptions were attributed to unlicensed indications and non-neuropathic painful conditions accounted for 80% of unlicensed gabapentin prescriptions and 50% of unlicensed pregabalin prescriptions [97], which has been confirmed in a recent UK study [94]. That is despite advice from Public Health England and the National Health Service England in 2014 [64].

### 4.5 Risks with Abuse of Gabapentinoids

At therapeutic doses, gabapentinoids seem to be well tolerated with the most common adverse effects from the central nervous system such as drowsiness, somnolence, dizziness, ataxia, and fatigue [89]. Withdrawal symptoms can be seen after immediate discontinuation of gabapentinoids suggesting physical dependence [20, 76, 77, 98, 99]. However, a recent study from Sweden [25] indicates that gabapentinoid users have an increased risk of suicidal behavior, unintentional overdoses, road traffic incidents, offences, and head/body injuries. This was seen to a higher degree in gabapentin users compared to pregabalin users. Pregabalin has also been associated with withdrawal symptoms following rapid discontinuation, which might be related to suicidal behavior [20, 100, 101]. When participants with substance use disorders in the Swedish study [25] were excluded, there were no associations with unintentional overdoses and road traffic incidents and offences. This might indicate that simultaneous substance use increases the risk, which is in agreement with research showing that gabapentinoid misuse is higher among people who misuse opioids [64]. Moreover, overdoses of gabapentinoids are associated with respiratory depression and cardiac insufficiency if combined with sedatives and opioids [48, 78]. Caution seems warranted when prescribing gabapentinoids to young people, especially those with substance use disorder as associations with adverse outcomes in general are mainly shown in younger age populations [25].

Several case reports and case series have been published describing non-fatal overdoses of gabapentinoids, most of them including other pharmaceuticals and often with blood supratherapeutic drug concentrations [47]. Similar findings have been found in DUID suspects [61]. Regarding fatalities after overdoses of gabapentinoids, there a number of retrospective studies from regional or national post-mortem toxicology registers in Finland [56–58] Sweden [30], Germany [102], and the UK [54]. The trend is that there is an increasing number of fatalities over the last 15–20 years in which gabapentinoids have been involved, mainly pregabalin. In almost all cases, other drugs have been found, mainly opioids, benzodiazepines, alcohol, and antidepressant drugs. In relation to sales, Ojanperä et al. [56] found that the Finnish number of deaths per million defined daily doses per year for pregabalin had an increasing trend from 2005 to 2013. Using this method for ranking the safety of 70 pharmaceuticals, pregabalin and gabapentin were ranked in the middle. An Irish study found an increase in the pregabalin poisoning deaths from 2013 to 2016 [51]. For gabapentin, it is still somewhat controversial whether a substantial overdose of gabapentin used alone is enough to induce life-threatening respiratory or cardiac insufficiency. There have been post-mortem cases describing self-poisoning with gabapentin alone [103, 104]. Pregabalin overdosing may have fatal consequences, especially if combined with opioids and sedatives [54, 56, 62]. In summary, overdoses of gabapentinoids alone seem to be relatively well tolerated but can be lethal if combined with other drugs of abuse, such as opioids and sedatives.

### 4.6 Recommendations to Healthcare Providers

Like opioids or benzodiazepines, gabapentinoids are often used to treat conditions in which treatment efficacy is generally based on subjective measures (Fig. 1). Patients might, intentionally or unintentionally produce or overstate symptoms to obtain new prescriptions or higher doses [68, 105]. It is important for prescribers to be aware of patients at risk of developing substance abuse. Patients with psychiatric disorders or substance use disorder (opioid abuse in particular)

- Health care professionals and health care providers must be aware of the misuse and abuse potential of pregabalin and gabapentin.
- Avoid if possible prescribing to patients belonging to risk populations such as psychiatric disorders or substance use disorder.
- Monitor signs of misuse and abuse in patients using these drugs.
- When new gabapentinoids are introduced on the market, the potential for misuse and abuse should be carefully investigated.

**Fig. 1** Recommendations to healthcare professionals and healthcare providers

seem to be at an increased risk. Therefore, prescribers and other healthcare professionals need to monitor signs of abuse or diversion in these patients [41]. Indicators of abuse might be requesting specific drugs, higher doses, or prescriptions from multiple sources, and claiming medications were lost. Given the frequent abuse and misuse of gabapentinoids, standard urine drug screening should include these substances [68]. In particular, patients undergoing opioid abuse treatment should be monitored in this manner. Moreover, it has been noted that individuals have admitted gabapentinoid abuse based on the knowledge that routine urine screening normally does not detect these substances [49, 72, 106].

Other important measures to reduce the risk for potential abuse are limiting quantities prescribed, adequately managing pain disorders, prescribing off-label cautiously, and preventing withdrawal symptoms by tapering gabapentinoids if discontinued. Thus, clinicians should be cautious about prescribing gabapentinoids and must consider whether the benefits outweigh potential harms in the individual patient. Regarding off-label use, a recent review [96] concluded: "Finally, guidelines, review articles, and point-of-care resources should more explicitly note the limited evidence supporting gabapentinoid use for off-label indications and should resist promoting gabapentinoid use for any pain labelled as neuropathic." One issue not so often taken into consideration is the documentation of the treatment effect of gabapentinoids also in conditions where they are approved. One recent review of pregabalin in the management of neuropathic pain [107] concludes that pregabalin has a beneficial effect on some symptoms of neuropathic pain, but its use is associated with a number of adverse events and the overall quality of evidence supporting its use is low. The authors advocate a need for larger, robust, high-quality clinical trials with particular attention paid to minimizing selective reporting of outcomes. They also noted that the studies were usually short with a median duration of 9 weeks.

### 4.7 Recommendations to Authorities

Correlations between an increased prescription of gabapentinoids and an increased frequency of abuse/misuse [45], and between the numbers of dispensings of pregabalin and pregabalin-positive poisoning deaths [51] have been reported. In the USA, the increased pregabalin use has also been related to 'off-label' use as an alternative to opioids for various pain management [108]. Moreover, Rossow and Bramness [109] have shown that the consumption of prescription drugs with an abuse potential is skewedly distributed and that few excessive users account for a disproportionately high proportion of the drug sales.

To limit the non-medical off-label use of gabapentinoids, restrictions in prescription and use have been implemented. For example, pregabalin and gabapentin have been classified as a scheduled class C drug in the UK in 2019 [110], meaning that the prescriptions do not allow multiple dispensions and prescriptions are valid for just 1 month. The medical profession supported this change despite an extra burden for prescribers, pharmacists, and patients [111]. National e-prescription systems have also been proposed to prevent altered prescriptions or overlapping multiple prescriptions [112–114], especially prescription of central nervous system anti-depressant drugs from different prescribers [51].

Authorities should stimulate the reporting of suspected adverse drug events such as abuse and misuse of gabapentinoids and support researchers to analyze such data as well as other healthcare registers. A new interesting possibility is to analyze wastewater to study substance consumption, which provides a picture of changes, over time and between different areas, in the total consumption, including non-prescribed use [115].

## 5 Conclusions

The gabapentinoids, pregabalin and gabapentin are abused and misused particularly by those with a history of drug abuse. Those with an opioid use disorder seem to be more prone to abuse gabapentinoids than patients with other substance use disorders. Gabapentinoids are widely used in conditions where they are not approved and in higher doses than recommended. It seems that pregabalin is the preferred drug by abusers owing to pharmacological differences compared with gabapentin. Intoxications with gabapentinoids are characterized by an intake of other psychoactive substances as well and there seems to be an increasing number of fatalities over the last years. Most often, the gabapentinoids are obtained from healthcare providers. Physicians and healthcare providers have to find methods to avoid prescriptions of gabapentinoids to patients with a risk of abusing drugs. Clinical guidelines may have to be reviewed and further restrictions for off-label prescription might need to be considered.

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