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Review Article

Gabapentinoid Use Disorder: Update for Clinicians

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Abstract

Gabapentinoids (gabapentin and pregabalin) are versatile drugs, indicated mainly for epilepsy and neuropathic pain, and have long been viewed as agents with little potential for abuse. Burgeoning prescribing patterns and studies indicate that these drugs are increasingly being abused, particularly by polydrug abusers who also abuse opioids. Gabapentinoid abuse is found in less 2% of the general population but may be as high as 15% to 22% among opioid abusers. Other risk factors for gabapentinoid abuse are less clear-cut but include mental health disorders. Gabapentinoids are relatively easy for drug abusers to obtain and many clinicians are not fully aware of their abuse potential. It is thought that gabapentinoids may offer psychoactive effects or enhance the effects of other drugs of abuse. Those who discontinue gabapentinoids abruptly may suffer withdrawal symptoms, but gabapentinoid overdose fatality is rare. Since gabapentinoids are often prescribed off-label to treat psychiatric disorders, these drugs may be dispensed to a particularly vulnerable population. Clinicians must be aware of the potential for Gabapentinoid Use Disorder: Update for Clinicians.

Keywords: *Gabapentin Abuse; Pregabalin Abuse; Gabapentinoid Abuse; Psychoactive*

Introduction

Even up until recently, gabapentin and pregabalin were not viewed as drugs that had much potential for misuse or abuse [1]. The literature describes a typical pattern in which a drug is first found to be effective and unlikely to be abused and then, after being widely prescribed, is found to have abuse potential [2]. Benzodiazepines followed this trajectory [3] and it appears that gabapentin and pregablin may follow suit.

Anecdotal reports presented in the literature suggest that the appeal of gabapentinoids involves their psychoactive effects (euphoria, dissociation) which can be achieved by taking large doses combined with relatively easy accessibility and low costs [4]. The earliest reports of potential misuse and abuse of gabapentin came from Europe, published in 2012 describing activity that took place in 2009 [5]. In France, the first pregabalin-related cases of abuse and dependence were reported in 2010 [6]. While it appears at first glance that these drugs may be more frequently misused in Europe, that pattern is shifting toward wider abuse in the United Sates. Gabapentinoid abuse typically involves combining either gabapentin or pregabalin with other drugs of abuse, such as opioids and/or cocaine, in order to potentiate or otherwise enhance the psychoactive effects of those drugs of abuse [7,8]. Although less frequently observed, gabapentinoids may also be abused by themselves, with psychoactive effects that have been described as calming, relaxing, and/or associated with euphoria [5].

Pregabalin and gabapentin are widely prescribed drugs and prescriptions for them have increased markedly, about 24% per year since 2004 [9]. Indicated mainly as anticonvulsants and considered effective against neuropathic pain and fibromyalgia, they have myriad off-label uses, including for acute pain, anxiety disorder, and nonspecific pain. Prescribers must be cognizant of the abuse potential of these drugs, particularly for the subset of patients with substance abuse disorders. In the United Kingdom, fatalities involving gabapentin or pregabalin increased from less than one per year in 2009 to 137 in 2015 [9]. The United Kingdom (UK) government is working to reclassify these two drugs as Class C controlled substances [10].

Methods

The authors searched "pregabalin abuse" and "gabapentin abuse" in PubMed and retrieved 146 and 263 results, respectively, with some duplication among results. The authors limited results to papers published in English and gave special emphasis to papers published in the past five years. Although we considered papers from all parts of the world, the authors were particularly interested in U.S. studies. This is a narrative and not a systematic review.

Gabapentin and Pregabalin

Both gabapentin and pregabalin-the gabapentinoids-are structural analogs of the γ-aminobutyric acid (GABA) mammalian neurotransmitter and are alpha-to-delta (α2δ) ligands [11]. It is thought they inhibit neuronal excitability and, in that way, reduce ectopic neuronal activation of hyperexcited neurons while allowing normal activation to remain unaffected. A growing body of literature suggests there is an abuse potential for gabapentinoids [12], which is not widely appreciated by healthcare professionals. A short summary comparison of gabapentin and pregabalin appears in table 1.

	Gabapentin	Pregabalin
Approved in USA	1993	2004
Indications in USA	Post-herpetic neuralgia Partial seizures with and without secondary generalization in patients > 12 years with epilepsy	Neuropathic pain associated with diabetes Post-herpetic neuralgia Partial seizures Fibromyalgia Neuropathic pain following spinal cord injury
Indications in Europe	Same as above plus neuropathic pain	Neuropathic pain Epilepsy Generalized anxiety disorder
Controlled substance?	No	Schedule V in USA
Bioavailability	Decreases with increasing doses	>90% even at higher doses
Peak serum concentration after oral intake	About 3 hours	About 1 hour
Potency	Less	Greater
Abuse	Less likely	More likely (faster absorption, more rapid onset of action)
Off-label uses	Pain related to diabetic peripheral neuropathy Restless leg syndrome Post-traumatic stress disorder Migraine headache Menopausal symptoms Alcohol and substance dependence and others	Chronic low back pain Benzodiazepine dependence Post-traumatic stress disorder Alcohol dependence Hypnotic-dependent insomnia Bipolar disorder and others
Recommended dose	900 to 3600 mg/day (divided into three doses per day; also available in a once-daily dose)	160 to 600 mg/day (divided into two or three equal doses per day)

Table 1: *Comparison of gabapentin and pregabalin [12-23].*

Gabapentin

Gabapentin, with the molecular formula $C_9H_{17}NO_2$, limits the inflow of calcium into the cells by binding to voltage-gated calcium channels [24]. Calcium allows for the release of neurotransmitters, modulates neuronal excitability, and activates certain secondary messenger pathways [25]. Although structurally similar to GABA, it does not affect $GABA_A$ or $GABA_B$ radioligand binding nor is it converted into GABA or a GABA agonist [26]. Gabapentin does not inhibit GABA uptake or degradation and, likewise, gabapentin does not alter the cellular uptake of dopamine, noradrenaline, or serotonin. Gabapentin does not undergo extensive metabolism in humans and is eliminated via the kidneys as unchanged drug. Its elimination half-life is five to seven hours and does not vary with dose or multiple doses. Its renal clearance is proportional to creatinine clearance in the patient. As such, gabapentin doses must be adjusted for patients with renal dysfunction [26].

The bioavailability of gabapentin is not dose proportional; its bioavailability is 60%, 47%, 34%, 33%, and 27% for daily doses of 900, 1200, 2400, 3600, and 4800 mg (administered as three doses per day). Thus, bioavailability decreases with dose increase. There is only a slight effect in the rate and extent of gabapentin absorption (14% increase in AUC and C_{max}) when the drug is taken together with food [26].

In the United States, gabapentin is approved for post-herpetic neuralgia and epilepsy [24] and is usually described as an anticonvulsant. Gabapentin is used off-label for many conditions, including pain control for various neuropathic conditions, psychiatric symptoms, restless leg syndrome, and substance-abuse disorders [27].

Gabapentin is available in capsule, tablets and oral solution [24]. The FDA-recommended maximum dose per day is 3,600 mg [24]. Symptoms of supratherapeutic doses may include mild sedation, nausea, dizziness, somnolence, and loose stools; gabapentin overdose fatalities are rare but have been reported [28,29].

Pregabalin

The molecular formula for pregabalin is $C_8H_{17}NO_2$; it is the active (S)-enantiomer of 3-(amino-methyl)-5-methylhexanoic acid. Pregabalin is a structural analog of GABA that does not appear to interact with GABA-A or GABA-B receptors nor is it converted to GABA or to a GABA-agonist. It likewise appears to have no effect on GABA uptake or GABA degradation. It binds selectively to α2δ subunits in voltage-dependent calcium channels found in hyperexcited neurons [30-32]. This binding reduces the action potential and thus the influx of calcium through the calcium channels which, in turn, reduces the release of certain neurotransmitters from the nerve terminals, such as glutamates and monoaminergic neurotransmitters [30,33]. Among other locations, pregabalin binds to the cortex, olfactory bulb, hypothalamus, amygdala, hippocampus, cerebellum, and dorsal horn of the spinal cord [30]. It is believed that the α2δ binding action of pregabalin is responsible for its anxiolytic effects [34].

Like gabapentin, pregabalin has negligible metabolism in humans and is excreted from the body in the urine largely unchanged (< 2% of the dose can be recovered as metabolites in the urine) [35]. Its main metabolite is an N-methylated derivate of pregabalin. Pregabalin is structurally similar to GABA, but does not bind to $GABA_A$ or $GABA_B$ or at benzodiazepine receptors. Pregabalin does not act as a sodium-channel blocker nor does it affect cyclooxygenase activity; pregabalin does not inhibit reuptake of dopamine, serotonin, or noradrenaline. Its elimination half-life is about 6.3 hours in patients with normal renal function, with peak plasma concentrations occurring at about 1.5 hours. Pregabalin elimination appears to be proportional to the patient's creatinine clearance. Oral bioavailability of pregabalin is ≥ 90% and is not dose dependent. Pregabalin absorption can be affected when the drug is taken with food, resulting in a clinically irrelevant 25% to 30% decrease in C_{max} and an extended T_{max} (approximately 3 hours). The pregabalin package insert advises that the drug can be taken with or without food. Compared to gabapentin, pregabalin has a faster and more predictable absorption in the gastrointestinal tract.

Pregabalin is available in a capsule to take orally and as a liquid that can be taken with an oral syringe; recommended dosing depends on the indication, with up to 600 mg/day allowable for epileptic adults but lower doses in adults with fibromyalgia or diabetic neuropathy (300 mg/day) [36].

Prescribing Patterns

Gabapentin and pregabalin have several important approved indications and are widely used off-label, so they are frequently prescribed agents. Since they are not strongly associated with toxicity, adverse effects, or drug-drug interactions, clinicians may prescribe them liberally to a range of patients and at doses above the recommended therapeutic range. This had led to increasing numbers of prescriptions and patients taking these drugs at supratherapeutic doses. The pattern of abuse (documented in the literature with respect to prescription opioids) is that a very large amount of the drug is consumed by a very small number of patients, with very high average daily doses for certain patients. Consumption patterns of gabapentinoids recently reported in the literature are suggestive of abuse, albeit to a much lesser degree than that currently seen with opioids [37]. In an observational drug utilization study from the United Kingdom, a cohort of 18,951 patients was studied who had been prescribed pregabalin; dosing information was available for 71% of them (n = 13,480) [38]. Most patients were female (60.1%), median age was 58 years, and the median prescribed average daily dose of pregabalin for all patients was 150.0 mg/day. Epileptics were prescribed the highest doses (191.9 mg/day) followed by patients with neuropathic pain (158.0 mg/day), and generalized anxiety disorder (150.0 mg/day). The maximum approved dose of pregabalin is 600 mg/day and only 1.0% of patients (n = 136) were prescribed more than that. Of this subset of 136 patients prescribed supratherapeutic doses, 18.4% had a history of substance abuse compared to a 14.0% incidence of substance abuse in the entire patient cohort [38].

A pharmacoepidemiological drug utilization study in Denmark explored "high use" (≥ 600 mg/day) and "very high use" (≥ 1,200 mg/day) over six and 12 months to identify patient characteristics associated with these doses [39]. This study (n = 42,520 pregabalin users) found 9.6% were "high use" and 6.5% were "very high use" for over 12 months. Risk factors for these use patterns were male sex and concomitant prescription(s) for benzodiazepines or antipsychotic agents [39]. In the United States (US), gabapentin diversion rates have increased from about zero in the first half of 2002 to a high of 0.027 cases per 100,000 population in the fourth quarter of 2015 [40].

Misuse/Abuse

GABAergic properties are thought to play a role in drug addiction [41,42]. Preclinical studies revealed that pregabalin modulated the GABA and glutamate systems, which may have at least suggested abuse potential [43]. GABA-modulating properties are present in many substances of abuse, such as alcohol, benzodiazepines, and the hypnotic "Z-drugs" [44]. Gabapentinoids may affect the body's dopaminergic system [45].

Although euphoria has been reported as an adverse effect of pregabalin [46], it was not observed in many studies [47]. At very high doses, psychotic experiences, hallucinations, and suicidal ideation may occur with pregabalin [48].

In a systematic review, gabapentin misuse and abuse was found to be about 1% in the general population but about 15% to 22% among opioid abusers [49]. Of individuals with a prescription for gabapentin, about 40% to 65% were misusing or abusing gabapentin. Misuse was reported either for its psychoactive effects (recreational purposes), self-medication, or, less frequently, to harm oneself [49]. The psychoactive effects of gabapentinoids include: sedation, relaxation, feeling of contement, numbness, disinhibition, enhanced sociability, greater empathy, audio and visual hallucinations, euphoria, and dissociation [4,50,51].

Gabapentinoids are typically taken intact orally (or orally by syringe) but other routes of administration have been described, including crushing and taking orally, smoking, insufflation ("snorting"), injection, rectal administration, and "parachuting" (wrapping crushed medication in toilet paper and swallowing whole to absorb large quantities of the drug without tasting it) [52].

While gabapentinoid misuse and abuse appears most associated with other drugs, the literature reports cases of individuals who become dependent on these drugs in monotherapy [53]. As with opioid-dependent individuals, individuals who become dependent on gabapentinoids have reported cravings [54-56].

Withdrawal

Gabapentin withdrawal is associated with symptoms similar to those of benzodiazepine withdrawal, involving disorientation, anxiety, insomnia, heart palpitations, diaphoresis, stomach cramps, and others [57-59]. In one study, about a third of pregabalin abusers suffered withdrawal symptoms when the drug was discontinued abruptly [51]. Benzodiazepine administration during withdrawal does not appear to relieve withdrawal symptoms [54,59]. A case report of a psychiatric patient who abused alcohol, benzodiazepines, and pregabalin (up to an average of about 750 mg/day with occasional use over 1,000 mg/day) reported severe anxiety and tension when he could not obtain pregabalin. He often managed these symptoms by drinking and use of benzodiazepines [60]. He underwent inpatient detoxification and experienced insomnia, sweating, nervousness, and anxiety during the withdrawal period [60].

Studies Quantifying Misuse/Abuse of Gabapentinoids

The misuse of gabapentinoids is increasingly being quantified in a variety of surveys and retrospective studies; see table 2. Misuse and abuse of gabapentinoids appears to be related to polydrug abuse, and is not trivial. In a systematic review of 59 studies (24 epidemiological studies, 3 clinical abuse liability studies, 16 case reports/case series, and 17 acute overdose case reports/case studies), a 1.6% prevalence of gabapentinoid abuse in the general population was observed; however, among opioid abusers, the prevalence of gabapentinoid abuse ranged from 3% to 68% [13]. While gabapentin and pregabalin are often abused by individuals abusing other drugs, such as opioids, the literature reports a case study of pregabalin abuse with no other drugs (other than cigarettes) [56].

Study Location	Drugs	Inclusion Criteria	Methods	Results
Alblooshi 2016 Survey (n = 250) United Arab Emirates	Pregabalin	Cohort of male substance abuse patients from the National Rehabilitation Center	Questionnaire completed in interview setting	84.4% were polydrug abusers; 68% used pregabalin
Baird 2014 Survey (n = 129) Scotland	Gabapentin, pregabalin	Patients at substance misuse clinics (methadone maintenance)	Self-report survey	22% used gabapentinoids and of these, 38% said they took them to enhance the psychoactive effects of methadone
Chiappini 2016 (n = 115,616) Europe	Gabapentin, pregabalin	Gabapentinoid misuse and dependence in European Medicine Agency Spontaneous Adverse Drug Reaction Reporting System	Retrospective database study	6.6% of pregabalin reports involved misuse, abuse, or dependence; 2.05% of pregabalin patients died; 4.77% of gabapentin reports involved misuse, abuse, or dependence and among users, 21% died
Hakkinnen 2014 Retrospective from 2010-2011 Finland	Gabapentin, pregabalin	Pregabalin or gabapentin was found in toxicology reports	Postmortem toxicology samples, database, death certificates, patient histories. Drug abuse was determined if patient was a known drug abuser or if injection marks were observed or if injection equipment was found near the body or if other illicit drugs were detected in the toxicology reports	Drug abuse was determined in 48.1% of pregabalin and 18.6% of gabapentin cases. Median blood concentrations in drug abusers were 15 mg/L and 5.8 mg/L for pregabalin and gabapentin, respectively.
Kapil 2014 Internet survey (n = 1500) 2011-2012 UK	Drug use, including gabapentin and pregabalin	16-59 years old, UK residents only	Survey to global consumer panel	Lifetime prevalence of misuse of gabapentin and pregabalin were 1.1% and 0.5% respectively, while lifetime prevalence was 8.1% for cocaine and 28.1% for cannabis. Of those misusing a gabapentinoid, 13.1% said their prescription was their sole source.
Kriikku 2014 (n = 3863) Retrospective study of DUID drivers in 2012 Finland	Pregabalin, benzodiazepines, cannabis, stimulants, opioids, alcohol	Drivers suspected of DUI in Finland	Blood samples analyzed by LC-MS/MS	206 cases had pregabalin at levels >0.68 mg/L, median was 6.2 (range 0.68-111.6) mg/L. In 3 cases, pregabalin was the only psychoactive agent detected.
Lyndon 2017 (n = 30) UK	Gabapentin, pregabalin	Drug-related deaths from 2004 to 2015 that mention both an opioid plus gabapentin or pregabalin plus interviews from individuals with a history of polydrug abuse involving heroin	Interviews and database study	Deaths involving gabapentinoids increased from <1/year in 2009 to 137 in 2015 (79% of these fatalities involve opioids). Heroin users reported that pregabalin was easy to obtain and enhanced the effects of heroin.
Mersfelder 2016 Systematic review of case reports and case studies (n = 18) USA	Gabapentin	Addiction or withdrawal	Systematic literature review	All addiction cases involved patients with history of alcohol, cocaine or opioid abuse; patients on average took 3000 mg/day (600 to 8000 mg/day range).
Peckham 2017 Truven Health MarketScan® commercial claims and encounters database 2013-2015 USA	Gabapentin, pregabalin, opioids, alprazolam, zolpidem	Patients with ≥ 2 claims for at least one abusable drug and ≥12 months continuous enrollment. Prevalence analysis was limited to those with ≥120 days of therapy	Abuse potential measured by Lorenz-1 (consumption of drug supply by top 1% of users) ≥15%	Lorenz-1 values were: Opioids 37% Gabapentin 19% Pregabalin 15% Alprazolam 14% Zolpidem 13%. The top 1% of gabapentin users filled prescriptions for a mean of 11,274 mg/day (median 9,534 mg/day).
Wilens 2015 Survey (n = 196) USA	Gabapentin, pregabalin, opioids, alcohol, other drugs of abuse	Opioid abusers seeking detoxification (not all were opioid dependent)	Self-report questionnaire	11% and 5% used gabapentin and pregabalin, respectively, without prescription; gabapentin and pregabalin use was higher among opioid-dependent patients (22% and 7%, respectively). Half (50%) of those prescribed pregabalin used more than the prescribed doses
Wills 2014 Retrospective study of data from poison center (n = 347) USA	Gabapentin, pregabalin, other anticonvulsants	Overdose patients excluding children and polypharmacy patients	Retrospective database study	No deaths from gabapentin or pregabalin

Table 2: *Retrospective database studies and surveys of pregabalin and/or gabapentin abuse [7,9,12,15,16,37,61-65]. Studies appear in alphabetical order by first author.*

The Association Between Gabapentinoid Abuse and Opioid Abuse

The prevalence of gabapentinoid abuse ranges from 3% to 68% among those known to abuse opioids, although the prevalence of gabapentinoid abuse in the general population is 1.6% [13]. A study from Germany found that 12.1% of patients treated for opioid addiction had abused pregabalin [66]. In a retrospective database study, 42% of patients who simultaneously consumed opioids, pregabalin, and gabapentin for 120 days or more had at least three claims exceeding the dose threshold for those drugs over 12 months. For those simultaneously taking both an opioid and gabapentin only, 24% had at least three claims in 12 months exceeding the dose threshold [37]. In a 2015 study of opioid abusers, the concomitant recreational misuse of gabapentin increased 165% versus 2015 and 2,950% since 2008 [67]. However, gabapentinoid abuse appears less frequent among those who abuse substances other than opioids. In a study of opioid abusers treated for addiction, 22% had previously abused gabapentin and 7% pregabalin; in that same study, no patients treated for other addictions had ever abused gabapentinoids [63]. However, there have been reports of associations between gabapentinoid misuse and cocaine abuse [68] and benzodiazepines abuse [67]. On the other hand, alcohol does not seem to be associated with gabapentinoid abuse [63].

The reasons for this apparent association between opioid abuse and gabapentinoid abuse remain to be elucidated. Many opioid addicts are polysubstance abusers. It has been suggested that gabapentinoid abuse among opioid addicts may owe in part to the fact that the former is far more easily accessible and thus they may supplement their drug regimens when opioids or other drugs of choice are harder to obtain [67]. Gabapentinoids are considered fairly easy to obtain and relatively inexpensive. Additionally, few urine assays routinely screen for gabapentinoids, making them easy drugs to conceal in random drug tests. It has also been suggested that a subset of opioid abusers is self-medicating for high levels of pain and gabapentinoids may help with analgesia [69]. Another explanation for the putative link between opioid abuse and gabapentinoid abuse involves those users who report taking gabapentinoids in order to potentiate the effects of opioids [7,8,66,69].

Polydrug abuse is prevalent among opioid addicts. In a study of 82 opioid-maintenance patients, consecutively collected urine samples ($n = 200$) were analyzed using a liquid chromatography/time-of-flight mass spectrometry screening to detect a variety of potentially abused drugs [70]. Of the 200 samples, polydrug abuse (defined here as ≥ 3 drugs in one sample) occurred in 40% of assays. Pregabalin was detected in 4% of the samples [70].

In a retrospective study of 196 admissions to a public detoxification program in the U.S., 162 patients were opioid dependent and statistically significantly more likely to misuse other prescription medications ($p < 0.0003$). In self-reports, 22% and 7% of these opioid-dependent individuals reported abusing gabapentin and pregabalin, respectively [63].

In a study of postmortem toxicology reports from Finland in which gabapentin or pregabalin was detected ($n = 359$), 48.1% of those with pregabalin in their systems at the time of death were considered to be drug abusers and of this group, 91.4% had detectable amounts of opioids in their system [16]. Conversely, of those gabapentin users deemed to be drug abusers, 87.5% had concomitant opioids [16]. While gabapentinoid abuse is more frequently reported in the literature based on international studies, US abuse of these drugs is likewise on the increase. In a 2016 study of 503 Appalachian Kentuckians currently reporting nonmedical use of opioids and not in any sort of rehabilitation program, 15% reported that they had used gabapentin in the past six months to "get high" [67]. This represents almost a 30-fold increase compared to 2008 in this cohort. Study subjects said they used gabapentin an average of 25 of the past 30 days. In this cohort, gabapentin use was reported significantly more often by women (77.8%) and those with chronic medical conditions (48.2%) [67].

Pregabalin was classified as a Schedule V drug meaning it posed a low risk for possible abuse or addiction, but since studies routinely exclude those who abuse opioids, they may have excluded a population most vulnerable to gabapentinoid abuse [66].

The Possible Role of Gabapentinoids in Treating Addiction

Since gabapentinoids may help attenuate opioid withdrawal symptoms, it has been speculated that these drugs are taken by opioid addicts to help manage their withdrawal symptoms [66]. Preclinical studies of pregabalin have raised the notion that it might be useful in treating addiction [43]. Pregabalin reduced the severity of withdrawal symptoms in opioid-dependent rats [71]. Since pregabalin affects the reward system in the brain, it may be associated with both addiction and recovery.

Since gabapentinoids modulate the α-2-delta (α2δ) subunit of voltage-gated calcium channels, they appear to exert protection against opioid tolerance and dependence. The mechanism behind this is not yet elucidated, but may involve an anti-inflammatory action [72]. In a murine study, it appears that gabapentin can upregulate the anti-inflammatory cytokine interleukin (IL) 10, which, in turn, inhibits other pro-inflammatory cytokines [72]. Combined with methadone or buprenorphine for opioid maintenance, gabapentin has been shown to mitigate withdrawal symptoms in opioid addicts [73]. There is promising preclinical evidence that pregabalin may also be able to prevent the development of morphine tolerance [71].

The literature reports the off-label use of gabapentinoids as pharmacological treatment of benzodiazepine abuse [74]. Benzodiazepine use disorder has no currently approved pharmacological treatment and the long-term abuse of benzodiazepines is associated cognitive impairment, which in some cases may be irreversible [75]. In a study of 14 long-term abusers of benzodiazepines (> 15 years), patients were administered pregabalin for substitution therapy. Side effects were mild and transient and all patients completed the study; all patients improved in certain measures of global cognitive functioning [18].

Oral pregabalin was shown in a preclinical study to reduce cocaine self-administration over 6 hours and relapse [76]. A systematic literature review however urges caution in terms of supporting this use for humans [77].

Gabapentin is currently being studied for its possible role in alcohol use disorder, which affects over 16 million American adults [78]. A literature review found 10 publications about the use of gabapentin for treating alcohol withdrawal symptoms and alcohol dependence with promising results and no severe adverse reactions [79]. Alcohol consumption is thought to stimulate the mesolimbic dopaminergic neurons, which originate in the ventral tegmental area and extend outward into the nucleus accumbens. Alcohol causes the release of dopamine into the mesolimbic system, but gabapentinoids appear to inhibit dopamine release. Gabapentin is thought to increase the brain's ability to synthesize GABA [80,81] and has produced promising results in studies ameliorating alcohol abuse [19,82,83]. Pregablin inhibits the release of glutamate, norepinephrine, and Substance P and has likewise been used with promising results to reduce cravings in alcohol abusers [84]. Since these gabapentinoids are agents that may themselves be abused, caution is advised in interpreting these results.

Dual Diagnosis

Higher abuse rates of gabapentinoids have been observed among psychiatric patients [63,69]. This is congruent with the observation that opioid addiction is prevalent among patients with mental health disorders (so-called dual diagnosis) [85] so this may be a particularly vulnerable population. Moreover, gabapentinoids are often prescribed, albeit off-label, for mental health conditions so this population may be more exposed to these agents and be administered relatively high doses. Of particular note is the fact that pregabalin may be prescribed (off-label in some parts of the world) to patients suffering from anxiety. Anxiety is, in and of itself, associated with elevated risk for substance abuse [86,87].

Prison Use

In general, prison populations are particularly vulnerable to drug abuse because prisons house a high proportion of people with psychiatric disorders and individuals with a criminal history are likely to possess attributes such as impulsivity and recklessness that could predispose them to drug abuse [88]. Depression and anxiety that are likely to be experienced by many incarcerated individuals may further contribute to the urge to self-medicate with any available drugs. While some drugs in the prison system are contraband, gabapentinoids may be prescribed for prisoners.

In the UK, prison system healthcare providers have reported that prisoners frequently request pregabalin for pain or for help overcoming opioid addiction [89]. Gabapentin misuse has been reported within the U.S. prison system [68]. In a survey of 250 former prisoners currently living in a correctional community center and having been referred for psychiatric evaluation, all patients reported some form of substance use disorder, 72% were polysubstance abusers, 58% had opioid use disorder, and 16% reported that they had misused/abused gabapentin in the past [69].

Harms

Gabapentinoid overdose is most frequently associated with such symptoms as hypotension, tachycardia, and central nervous system (CNS) symptoms [90], but a few fatalities have been reported in the literature [16,28]. Gabapentinoid overdose fatalities typically involve other drugs such as opioids. In a study of seven overdose deaths in Sweden involving the fentanyl analog furanylfentanyl, pregabalin was detected in 71% (5/7) of decedents [91]. The literature also reports a case of self-harm involving pregabalin ingestion [92].

Risk Factors for Gabapentinoid Abuse

Prescribers should be aware of the growing patterns of misuse and abuse of gabapentin and pregabalin evidenced by more and more prescriptions for higher, even supratherapeutic doses. Since gabapentinoids play a valuable role in the pharmacological armamentarium, risk stratification may be helpful. A systematic review of 59 studies identified two key risk factors for gabapentinoid abuse: a history of substance abuse (particularly, but not exclusively, opioid abuse) and mental health disorders [13]. In a Swedish study of pregabalin patients, risk factors associated with supratherapeutic doses of pregabalin were similar to those of opioid abuse: younger age, male sex, low income, history of substance abuse, consumption of high doses of other abusable drugs, and history of addiction [93]. A study from Denmark could draw the associations among high doses of pregabalin, male sex, and prescription for opioids, antipsychotics, and/or benzodiazepines [39]. These studies of patients who took doses greater than the maximum approved dose of a gabapentinoid did not evaluate the reasons for these high doses-abuse is a possibility, but there may be have been other factors as well.

Age as a risk factor for gabapentinoid misuse is harder to define. In a study of 440 patients undergoing substance abuse rehabilitation, pregabalin users had a median age of 38 years [94]. Among lethal intoxications, the median age of gabapentinoid abusers was 30 compared to 58 years for non-gabapentinoid-abusers [16]. In a study from Finland of suspected drugged drivers, pregabalin was found in 206 cases, of which 79.6% were drivers under the age of 40 [15]. However, the mean concentration of serum pregabalin was highest in older drivers, namely those between 50 and 59 years [15]. This study also suggests that polydrug abuse may be associated with pregabalin abuse in that 43.2% of these cases involved drivers with ≥ 5 drugs in their systems [15].

It is unclear whether men or women are at greater risk for gabapentinoid abuse. Male sex was identified as an independent predictor of *high dose use* of pregabalin [39]. Yet in a study of gabapentinoid misuse or dependent from the European Medicines Agency (EMA) and their EudraVigilance database, of the total reports, 6.6% were for pregabalin (n = 7,639) and 4.8% were for gabapentin (n = 4,301) with higher numbers of women than men in both groups [12]. In a pharmacoepidemiological study from Denmark of 42,520 adults prescribed pregabalin, more women than men (61%) had at least one prescription for pregabalin within the study timeframe of 2004 to 2013 [39]. However, this study quantified the number of prescriptions and did not evaluate actual misuse or abuse.

High doses of gabapentinoids do not necessarily indicate abuse, but should be reviewed carefully as a potential red flag. Risk factors for high doses of gabapentinoids have been described in the literature. In a retrospective database study of individuals dispensed at least three prescriptions for pregabalin between July 2006 and December 2009 (n = 48,550), the "daily dose" was defined as the amount of pregabalin dispensed in that period divided by the number of days between the second and third dispensings [93]. Those dispensed more than a 600 mg/day dose of pregabalin were evaluated using multivariate regression models to determine if there were specific factors associated with higher-than-approved doses. Of the total number of pregabalin patients, 8.5% were dispensed a dose > 600 mg/day. Of these patients, a previous addictive disorder drug treatment was present in 31% of those dispensed higher-than-approved doses. Other risk factors include male sex (adjusted odds ratio [aOR] 1.40, 95% confidence interval [CI], 1.31 to 1.49), age between 18 and 29 years versus ≥ 65 years (aOR 1.62, 95% CI, 1.45 to 1.82), low income (aOR 1.24, 95% CI, 1.10 to 1.40), epilepsy (aOR 1.41, 95% CI 1.10 to 1.81), prior substance use disorder diagnosis or treatment (aOR 1.41, 95% CI, 1.31 to 1.52) or previously dispensed high doses of other drugs with abuse potential (aOR 1.77, 95% CI, 1.62 to 1.94) [93].

How Abusers Obtain Gabapentinoids

Because knowledge of the inappropriate use of gabapentinoids is limited among healthcare professionals, these drugs are often prescribed and dispensed without particular concern about their potential for abuse. Since gabapentinoids are indicated for many conditions with subjective symptoms, skillful abusers may be able to deceive prescribers. Of those who abuse gabapentinoids, the majority (63%) report that they get them from healthcare professionals as prescribed medications, but supplement this with other sources, among them friends, families, and internet sites [62]. It appears that the boundary between "recreational user" and "patient with a prescription" is less well defined here than among other prescription drugs of abuse, such as opioids. Gabapentinoid abusers may also rely on the familiar strategies employed by other prescription drug abusers: doctor shopping, falsifying symptoms, asking for early prescription refills, claiming to have lost their pill supply, and so on [95]. In a study of opioid abusers in Appalachian Kentucky (n = 503), 15% reported having used gabapentin at least once in the past 30 days. Their main sources of the drug were physicians (52%) and drug dealers (36%) [67]. Online sources should be considered as well. A Google search conducted in September 2017 for "buy pregabalin without prescription" and "buy gabapentin without prescription" turned up 352,000 and 1,190,000 results.

Clinician Guidance

In light of the emerging information about gabapentin and pregabalin, healthcare professionals need to learn more about the abuse potential of these agents. Gabapentinoids are important drugs and there is no benefit in withholding them from patients who truly benefit from their use, such as epileptics or individuals suffering from neuropathic pain syndromes. Tolerance with longtime exposure as well as individual clinical considerations may sometimes necessitate high doses of these drugs. However, there are clear patterns that these drugs are being misused and abused. It remains to be proven that the recent decrease in opioid prescribing may be somehow associated with the increased use of gabapentinoids.

Clinicians should understand the appropriate indications for gabapentinoids. Off-label prescribing of gabapentin and pregabalin must be carefully considered. It may be better to refer patients with persistent complaints about pain to pain specialists instead of offering them gabapentinoids [54]. The same applies to patients with anxiety and other mental health conditions, who may be better served with a referral to a psychiatrist than a prescription for gabapentinoids. Truly, gabapentinoids are versatile agents, but this versatility makes them easier for abusers to obtain (by falsifying subjective symptoms) and clinicians should be concerned about prescribing them to potentially vulnerable populations, namely those with mental health conditions.

It appears that the most clear-cut risk factor for gabapentinoid abuse is opioid abuse. Sound, but professionally compassionate clinical judgment is always necessary when treating patients with active substance abuse disorders. In particular, active or a recent history of opioid misuse and abuse must be considered a risk factor for potential gabapentinoid abuse. Such patients should be counseled and, if appropriate, referred to specialists. Many who misuse and abuse opioids are not forthcoming with healthcare professionals, so prescribers may need to ask difficult questions and evaluate responses critically. Gabapentinoids may be more attractive to potential drug abusers than clinicians realize: they are considered among abusers to be easily available, they are relatively inexpensive, and they are often not detected in urine screening tests. For that reason, specific screening assays for gabapentinoids administered at random may be helpful to detect abuse.

It is interesting to note that gabapentinoids may be used by some opioid abusers to help manage withdrawal symptoms; patients who are struggling with opioid dependence and addiction may be better served by being offered specific treatment rather than self-management.

Conclusion

Gabapentinoids, gabapentin and pregabalin, are important anticonvulsant agents that may offer a wide spectrum of appropriate uses, but prescribing patterns suggest these agents are increasingly drugs of abuse, particularly among opioid addicts. Paradoxically, gabapentinoids may also play a role in mitigating opioid withdrawal symptoms and are being explored in preclinical studies as pharmacological approaches to opioid, cocaine, benzodiazepine, and alcohol abuse. Gabapentinoids are considered fairly easy to obtain and relatively inexpensive. Additionally, few urine assays routinely screen for gabapentinoids, making them easy drugs to conceal in random drug tests. Clinicians should be aware that these widely prescribed agents are not without risk and may, indeed, be increasingly popular drugs of abuse in some patients.

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