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EDITORIAL

Heightened misuse risk and addictive potential of gabapentinoids: the fate of effective anxiolytics

Cuneyt Evren[1], Vahap Karabulut[1]

[1]Bakirkoy Training and Research Hospital for Psychiatry Neurology and Neurosurgery, Research, Treatment and Training Center for Alcohol and Substance Dependence (AMATEM), Istanbul - Turkey

Gabapentin and pregabalin, two pharmacologically very closely related substances, are classed as gabapentinoids (1). Gabapentin was synthesized in 1977 to create a structural analogue to gamma-aminobutyric acid (GABA) with a higher degree of lipophilia than the original neurotransmitter. In 1993, its use in the treatment of epilepsy began. Pregabalin, another structural analogue of GABA, was synthesized in 1991; in 2004, it was introduced for the treatment of neuropathic pain and in 2005 for the therapy of refractory epilepsy. A third member of this drug family, mirogabalin, is currently undergoing clinical trials for the treatment of diabetic neuropathy, fibromyalgia, and postherpetic neuralgia (2).

Gabapentinoids are commonly used in neurology, psychiatry, and primary healthcare. In Europe, pregabalin is used in the treatment of epilepsy (partial seizures), neuropathic pain, and generalized anxiety disorder. In the U.S.A., while it is not licensed for anxiety, it also has been licensed for fibromyalgia and postherpetic neuralgia. In addition, the molecule is often prescribed off-label for a number of clinical conditions, including post-traumatic stress disorder, somatoform disorders, bipolar disorder, alcohol or substance withdrawal processes, attention-deficit hyperactivity disorder (ADHD), insomnia, restless leg syndrome, borderline personality disorder, menopausal problems, chronic prostatitis, vertigo, itching disorder, migraine, trigeminal neuralgia, postoperative pain, and non-neuropathic pain disorders (3-5). It is estimated that off-label use of gabapentin makes up 83-95% percent of all gabapentin use, accounting for over 90% of sales (5). A diagnosis of non-neuropathic pains accounts for 80.4% of gabapentin and 58.3% of pregabalin off-label prescription (6). In Turkey, gabapentin has been licensed for the treatment of epilepsy and neuropathic pain, and pregabalin for epilepsy, neuropathic pain, generalized anxiety disorder, and fibromyalgia. Drugs containing pregabalin and gabapentin as active ingredients belonged to the category of controlled drugs distributed with a regular prescription; however, in April 2019 pregabalin was included in the category of green-colored (controlled medication) prescription (7).

The mechanism of action of gabapentinoids is not fully understood. A generally accepted opinion states that they bind to a subunit of voltage-gated calcium channels in neurons, the alpha-2-delta (α2-δ) protein, reducing central neuronal excitability. By binding to calcium channels, these drugs reduce the calcium influx into the neuron and subsequently the release of neurotransmitters, which is believed to contribute to their antinociceptive, anticonvulsant, and anxiolytic properties (8-10). While gabapentinoids are structural analogues of the primary inhibitory neurotransmitter GABA, they do not bind directly to GABA receptors, but they are assumed to possess GABA-mimetic properties (4,11). Therapeutic doses of gabapentinoids cause a slight increase in the extracellular GABA concentration in the human brain cortex. Accordingly, they show weak GABA-mimetic properties at the beginning of treatment and at higher doses, triggering relaxation and euphoria

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Correspondence: Cuneyt Evren, Bakirkoy Training and Research Hospital for Psychiatry Neurology and Neurosurgery, Research, Treatment and Training Center for Alcohol and Substance Dependence (AMATEM), Istanbul - Turkey
Phone: +90 212 543 65 65/21 19 **E-mail:** cuneytevren@yahoo.com

(12). In addition, pregabalin reduces the release of various neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide (13,14). A recent study shows that gabapentin is simultaneously a strong activator for voltage-gated potassium channels. Pregabalin has been shown not to activate these channels; at higher concentrations (≥10 μM), it actually inhibits them (15).

Pregabalin and gabapentin share a number of similar pharmacokinetic and pharmacodynamic properties such as a similar metabolic profile, negligible protein binding, renal excretion, and minimal drug-drug interaction. At the same time, the two drugs show significant differences in absorption. The bioavailability of oral gabapentin is dose-dependent. The maximum plasma concentrations of pregabalin after oral administration increase with the dose linearly (10). Gabapentin absorption falls from 68% after a 300 mg dose to 36% after a 1600 mg dose due to saturation absorption, while pregabalin reaches a bioavailability of 90% despite increasing doses (16). Gabapentin reaches the highest plasma concentrations 3 hours after oral intake, but these concentrations are dose-limited and can vary between individuals due to absorption processes (10). The peak blood concentrations of pregabalin, compared to gabapentin, are achieved fast, within 1 hour (17). Neither of the two drugs binds to plasma proteins. The level of hepatic metabolism is negligible and the drugs are mainly eliminated through renal excretion. Gabapentinoids have a fairly short half-life of around 6 hours and are excreted with the urine almost unchanged (98%) (10). While pregabalin interacts with the same binding area as gabapentin and has a similar pharmacological profile, its affinity and strength in binding to the α2-δ subunit are higher than those of gabapentin (4). Given that pregabalin has a 2.5 to 6 times higher potency, faster absorption, and higher bioavailability, its misuse risk is higher than that of gabapentine (18).

Gabapentin is safely tolerated in a very wide range of doses between ca. 800 and 1800 mg/day (5). Irrespective of clinical indications, the daily amount is administered in three doses per day. The daily dose of pregabalin can vary significantly, between 75 and 600 mg (13), which can be divided into 2 or 3 portions per day. The recommended maximum intake for pregabalin and gabapentin, administered in more than one dose, is 600 and 3600 mg/day, respectively (16). As the main drug-related adverse reactions to gabapentinoids are dizziness and drowsiness, simultaneous use of other drugs that share their CNS-depressing effects can be expected to increase these effects. It has been shown that pregabalin enhances the cognitive and motor effects of oxycodone, ethanol, and lorazepam (2).

Factors encouraging the use of pregabalin in psychiatry and addiction include its unequivocal, fast, and well documented efficacy in a number of psychiatric disorders characterized by anxiety as a fundamental symptom; a daily dose of at least 600 mg is safe and well tolerated, drug interactions are few, cytochrome P450 enzymes are not inhibited, and side effects are usually light and temporary (19). Studies researching the role of pregabalin in alcohol and benzodiazepine dependency found contradictory results in the treatment of withdrawal symptoms; however, they provided evidence for its efficacy in the prevention of relapses (20-22). Similarly, study data confirm the safety and efficacy of gabapentin as a new treatment for alcohol use disorder (23,24).

In contrast to the important place of both drugs in clinical use, a potential for misuse and addiction has also been found. Generally, when administered in therapeutic doses to patients with no history of substance abuse, the misuse risk of gabapentinoids appears to be lower than that of other prescription drugs such as benzodiazepines (e.g., opioids and stimulants) or alcohol and illegal substances (25,26). A study in England that was carried out in the age group 16-59 years found a lifelong prevalence of gabapentin and pregabalin in the general population of 1.1 and 0.5%, respectively (27). However, in patients with a substance use disorder, especially those with opioid abuse, the misuse of gabapentinoid is more common. Studies focusing on patients with opioid use disorder found a misuse rate of 15-22% for gabapentin and of 3-68% for pregabalin (16). A study analyzing both drugs in a post-mortem population demonstrated a widespread use of these substances together with opioids. Particularly in heroin users, pregabalin use is quite significant. The prevalence of pregabalin in heroin users (19.5%) is 4.1 times higher than in patients not using heroin (4.7%) (28). It has been shown that pregabalin can be used to increase the effects of heroin or in some individuals to reduce heroin use (29).

For pregabalin as well as gabapentin, reports of their abuse potential increasingly emerge. In 2011, pregabalin was among the 30 most frequently prescribed drugs in the U.S.A. (30). In England, within only 5 years the prescription of pregabalin and gabapentin increased by 350% and 150%, respectively (31). In parallel, gabapentinoids are found more readily on the black market, hence not requiring prescription. More importantly, mortality databases in England have shown

a correlation between pregabalin and/or gabapentin use and death. It was found, though, that most of the gabapentin victims (2/3 in 2012) had not been prescribed the medication (4). In 12.1% of urine samples taken routinely from individuals with opioid dependency in a German addiction clinic, pregabalin was detected in patients who had not received a prescription in the context of clinical indication (30). By now, a large number of cases have been reported related to gabapentin (32-36) and pregabalin (37-43) abuse or addiction. A cohort study made in France showed that the probability of misuse (defined as a higher-than-recommended daily intake) was greater in new pregabalin users (12.8%) compared to gabapentin (6.6%) and duloxetine (9.7%). After the first period of drug misuse, gabapentin led to a primary addiction in 11.6% of gabapentin abusers and in 10.7% of patients misusing pregabalin (44). These study data demonstrate that drug misuse entails an addiction risk related basically to the psychoactive characteristics of these substances. A range of anecdotal information suggests that these drugs are commonly used in prisons. In comparison with the general population, prescription of gabapentin and pregabalin in penitentiaries is twice as high (2.8%). In the light of this data, the UK began to include gabapentinoids among the class C controlled substances (45).

The mechanism of gabapentinoid abuse is not fully understood. It is hypothesized that both gabapentin and pregabalin directly or indirectly affect the reward system, which may typically produce effects related to the level of inclination towards substance addiction (46). With therapeutic doses, a euphoria rate of between 1 and 12% has been reported. At higher than therapeutic doses, they have sedative as well as dissociative/psychedelic effects (18). Pregabalin is a GABA analogue with a complex pharmacodynamic profile and can thus cause addiction behaviors similar to those caused by benzodiazepines. In addition, the pharmacokinetic pathways of the drug (faster absorption rates and high bioavailability levels) are important in the explanation of its addiction potential (3,47). Tolerance for gabapentinoid effects reportedly develop and diminish quickly (48).

Supratherapeutic doses may produce sedation, dissociation, relaxation, satisfaction, torpor, uncontrolled behaviors, enhanced sociability, empathy, or visual and auditory hallucinations (16). Related to gabapentin misuse, effects like euphoria, increased assertiveness and marijuana-like "high"/relaxation or "zombie-like" states can be experienced (49). Pregabalin can be considered an "ideal psychotropic drug" to reach specific mental states including effects of euphoria with alcohol/GHB/benzodiazepine-like effects and entactogenic sensations/dissociation or to cope with opiate/opioid withdrawal (4). It is generally taken together with other substances such as alcohol/gabapentin/benzodiazepines, cannabinoids/LSD/Salvia divinorum, heroin/opioids, or amphetamine/synthetic cathinone. While most people use these drugs orally, other ways of administration have been reported including injection, smoking in cigarettes, inhaling pulverized tablets, and rectal use (18). Misuse of pregabalin may involve doses 20 times higher than the recommended maximal dosage (50). Case reports relating to misuse found median doses of 2,100 mg (800-7.500 mg) for pregabalin and 3,600 mg (1.500-12,000 mg) for gabapentin (16). Pregabalin, though its pharmacodynamic characteristics are similar to those of gabapentin, appears to involve a higher risk of misuse or inducing addiction (18). The reason is very likely to be a different pharmacokinetic characteristic, given that at higher doses, in contrast with gabapentin, the plasma (and brain) concentrations of pregabalin increase linearly (2,10,12).

Depending on the user, different pregabalin doses can produce very different effects (18):

- 600 mg: stumbling, disorientation, increased physical and psychological sensitivity, driving problems, stutter and speaking problems, auditory and visual changes/hallucinations, double and blurred vision, loss of behavioral inhibitions, talkativeness, increased bodily energy, higher sexual performance
- 900 mg: strong feelings of intoxication, gait difficulty, altered sense of colors, slight euphoria
- 1.200 mg: torpor, euphoria, entactogenic sensations (leading to a feeling of being in harmony with oneself and one's surroundings)
- >1.500 mg (up to 5 g): uncontrollable somnolence, frequent hallucinations, high euphoria, frequent dissociative events, behavioral inhibition, anxiety, and compulsive motions

It has been reported that rapid discontinuation of high-dose pregabalin is related with withdrawal symptoms (e.g., insomnia, nausea, headache, or diarrhea), while tolerance for a quick tapering-off of the drug can develop fast (18,41). In patients having used pregabalin for a long period of time, however, symptoms can last for several weeks (51). The withdrawal symptoms that have been described resemble those of the discontinuation of benzodiazepines (including withdrawal seizures and delirium) or SSRI (52). It is assumed that the mechanism

of pregabalin withdrawal symptoms derives from an increase in the production of the enzyme responsible for GABA synthesis when the drug is stopped (53). Case reports have shown that common pregabalin withdrawal symptoms include diaphoresis, tachycardia, hypertension, tremor, diarrhea, agitation, anxiety, confusion, gastrointestinal distress, paranoia, auditory hallucinations, mutism, self-mutilation, and suicide attempts (39,51,53,54). Another case presentation reported that a patient with chronic renal failure 4 days after pregabalin withdrawal developed a tonic-clonic seizure (55).

There are also case presentations in the literature demonstrating similar clinical symptoms for the withdrawal of gabapentin (34,36,56,57). A review of 15 case reports found gabapentin withdrawal symptoms generally to be agitation (>50%), confusion-disorientation (43%), diaphoresis (36%), nonspecific gastrointestinal symptoms (23%), tremor, tachycardia, hypertension (18% each), or insomnia (14%). In some cases, akathisia, catatonia, and seizures occurred. In every single patient, withdrawal symptoms set on between 12 hours and 7 days after discontinuing the medication, in most cases between 24 and 48 hours. On average, the daily dose used had been 3,000 mg (600-8.000 mg/day) (58). In one case, withdrawal symptoms in a newborn were reported (59).

While there are numerous case reports available to guide the clinicians in the diagnosis of acute gabapentin and pregabalin withdrawal symptoms, evidence for the best treatment of these patients is still limited. In gabapentin withdrawal, restarting the drug was effective in alleviating the withdrawal symptoms, while in most cases benzodiazepine was not able to control gabapentin withdrawal symptoms (58). Ideally, in pregabalin withdrawal the drug should be restarted and then tapered off. Stopping pregabalin by reducing the dosage gradually over 1 week is considered clinically safe (51). However, in long-term users of pregabalin, symptoms can continue for several weeks; therefore, the importance of careful monitoring and gradual titration needs to be emphasized. It is also recommended to continue benzodiazepines until the withdrawal symptoms subside. Clonidine is one of the recommended drugs to support acute withdrawal of pregabalin (53,54). For patients planning to discontinue these drugs, Public Health England (PHE) also proposes a more gradual reduction to allay withdrawal symptoms. The highest reduction rate for gabapentinoids suggested in the PHE guidelines is 50-100 mg/week for pregabalin and 300 mg/4 days for gabapentin (60).

For a number of clinical conditions, pregabalin and gabapentin are still relevant as evidence-based therapies. In environments where substance detoxification can be adjusted (eg, inpatient treatments), using gabapentinoids for patients with symptoms of pain, anxiety and insomnia may enhance their compliance. Thus, patients who are likely to benefit from this medication should not be deprived of it. At the same time, emerging evidence underlines the necessity for physicians prescribing gabapentinoids to evaluate their patients and to adopt a conscious approach to the use of these drugs. Misuse as well as addiction issues have been reported for gabapentinoids, and the number of deaths associated with these substances is not insignificant (61). Clinicians need to be aware of the potential risk of abuse as well as of withdrawal symptoms. When considering the prescription of gabapentinoids for neurological or psychiatric disorders, the patient's substance use history has to be investigated thoroughly. Particularly in cases with a history of substance use, the use of gabapentinoids (esp. pregabalin) should be avoided or, if necessary, strict therapeutic and prescription monitoring are required. As soon as any findings of pregabalin or gabapentin abuse are established, necessary measures need to be taken.

As we have mentioned before, in the UK the classification for both pregabalin and gabapentin has recently been changed to class C controlled substances. In the US, while pregabalin is controlled as a Schedule V substance nationwide, only some states (Tennessee, Kentucky) classify gabapentin as a controlled substance. In Australia, on the other hand, both pregabalin and gabapentin continue to be distributed as Prescription Only medications (Schedule 4), which does not require specific controls regarding supply or possession of these substances – a status similar to that of e.g. statins or antibiotics (62).

Diversion and misuse may be related with a failure to use therapeutic doses adequate for the patients. This behavior may mistakenly be considered as an addiction. Similarly, patients who do not wish to discontinue the use because they benefit from the drug while using it within the therapeutic dose range should not be mistakenly considered as addicts. Finally, since in Turkey pregabalin has an indication for the treatment of generalized anxiety disorder and is even included among first-line treatments for this diagnosis in some guidelines, there is no convincing justification for the refusal to reimburse drug prescriptions written by a psychiatrist. In patients using these medications in quantities higher than the treatment dose, difficulties in providing the drug will put the patient and psychiatrists

in a difficult situation as the detoxification treatment consists in a gradual reduction and discontinuation of these drugs over time. Furthermore, psychiatrists are more likely to identify patients with high misuse or addiction risks and manage these conditions than members of other medical branches who prescribe gabapentinoids for diagnoses of neuropathic pain, fibromyalgia, and epilepsy. Training should be provided for these medical specialties where clinicians are offered information enabling them to recognize patients at high risk of abuse while at the same time allaying unwarranted fear of misuse that may prompt them not to prescribe or to prescribe inadequate doses for patients needing the drug.

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