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Review

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Are gabapentinoids addictive?

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ABSTRACT

Gabapentinoids (GBPs) are highly effective drugs used in the treatment of epilepsy, anxiety disorders, and particularly neuropathic pain. In recent years, their use has become a cause for concern as reports on their misuse have increased. Studies have been conducted to identify the patient groups that are prone to the drug's misuse. Additionally, the drug's use has been restricted in some countries. While GBPs are favored due to their efficacy in pain management, their potential for addiction has made them a drug that physicians are increasingly hesitant to prescribe. The aim of this study is to review the research on the addictive effects of GBPs, providing physicians with information on predictive tests and anamnesis data regarding the risk of addiction.

Keywords: Pain management, substance-related disorders, neuralgia, epilepsy, anxiety disorders, physicians

INTRODUCTION

The use of gabapentinoids (GBPs) has been increasing in recent years because of their broad indications and success in pain management. The consumption of GBPs has increased more than fourfold in the last decade. In high-income countries, the drug's consumption is six times higher than that in low-income countries.[1] However, because of the drug's potential for addiction, its use has been restricted in some countries. Substance dependence, which was considered a sin or crime in the 19th century, was classified as a disease by the World Health Organization in 1952, following scientific advancements. For the first time in 1980, with the diagnostic and statistical manual of mental disorders (DSM)-III, a distinction was made between substance abuse and substance dependence, emphasizing that physiological dependence symptoms are necessary for a diagnosis of addiction. In the DSM-IV, substance abuse was defined as a milder disorder compared with substance dependence and was considered an early stage of addiction. Moreover, tolerance and withdrawal were no longer required for a diagnosis of addiction. The category "disorders related to substance use" in DSM-IV was changed to "substance-related and addictive disorders" in DSM-V.[2] Substances associated with use disorders are categorized as alcohol, caffeine, cannabis, hallucinogens (phencyclidine and other hallucinogens), inhalants, opioids, sedative-hypnotics and anxiolytics, stimulants (amphetamines, cocaine, and other stimulants), nicotine, and other (or unknown) substances.[2,3] GBPs are in the sedative, hypnotic, and anxiolytic group.

As addiction progresses, not using the addictive substance leads to symptoms, such as anhedonia, anxiety, depression, dysphoria, and irritability, and the urge to consume the substance increases to alleviate these negative symptoms rather than for the primary reinforcement.[3]

Substance use does not necessarily result in addiction. The development of addiction is associated with environmental, neurodevelopmental, and genetic factors. Approximately 15–17 out of every 100 individuals who begin using a substance will develop an addiction.[3,4] Conversely, abuse refers to using a substance for purposes other than its intended use without necessarily developing an addiction.

In the literature, although the term addiction has been used in relation to GBPs in recent years, the term abuse has been used for a much longer period.

Gabapentin (GBP) and pregabalin (PGB) belong to the group of GBPs. GBP was approved by the United States food and drug administration (FDA) in 1993 for the treatment of post-herpetic neuralgia and epilepsy, and the drug holds an indication for neuropathic pain according to the European medicines agency (EMA). PGB was approved by the FDA in 2004 for the treatment of neuropathic pain, post-herpetic neuralgia, seizures, and fibromyalgia, and it holds an indication from the EMA for generalized anxiety disorder.[5] Moreover, the off-label use of GBPs is common. Off-label uses include

headache, trigeminal neuralgia, acute or chronic postoperative pain, chronic non-specific low back pain, fibromyalgia, anxiety disorder, attention deficit hyperactivity disorder, bipolar disorder, alcohol withdrawal, opioid withdrawal, sleep disorders (insomnia and restless legs syndrome), and pruritus.[6,7]

GBPs share a similar mechanism of action but differ in their pharmacokinetic and pharmacodynamic properties.[7] Although structurally similar to gamma-aminobutyric acid (GABA), GBPs do not bind to the same receptor. They bind with high affinity to the α2δ-1 subunit of voltage-gated calcium channels (VGCCs) as well as to the N-methyl-D-aspartate receptor, inhibiting both. This likely inhibits the release of excitatory neurotransmitters and synaptogenesis, possibly through thrombospondins. The α2δ-1 subunits of VGCCs play a role in nociception. Following injury, the number of α2δ-1 subunits increases. However, their reduction can take several months. In transgenic mice that express high levels of α2δ-1, neuropathic pain has been shown to develop even in the absence of nerve damage.[7,8]

MECHANISM OF ADDICTION FOR GABAPENTINOIDS

The frequent prescription of GBPs because of their broad indication profile has been accompanied by increasing reports of abuse and mortality.[9] Gabapentinoid-related mortality was first recorded in the United Kingdom's database in 2006.[9] GBPs exhibit GABA-mimetic properties and likely exert effects on the dopaminergic reward system.[9] Deficits in glutamate clearance and postsynaptic glutamatergic receptor activation are thought to be associated with drug-seeking behavior and chronic drug use.[10] Glutamate transporter type-1 (GLT-1) plays a crucial role in the reuptake of synaptically released glutamate and in drug-seeking behavior.[10] Althobaiti et al.[10] showed that the drug-seeking behavior induced in mice administrated with 60 and 90 mg doses of PGB was blocked by ceftriaxone, a potent GLT-1 upregulator, which was reported as concrete evidence of PGB's addictive potential.

GABAPENTINOID ABUSE

Not everyone who uses GBPs develops an addiction. However, a history of psychiatric illness and substance abuse increases the likelihood of GBPs abuse.[11] When taken intravenously, intranasally, or orally at doses higher than the therapeutic range, GBPs can cause euphoric and dissociative effects.[12]

Relaxation and euphoria, especially at the beginning of drug treatment and at overdose, are due to the weak GABA-mimetic properties of GBPs and may lead to tolerance.[13]

Individuals with substance use disorder (SUD) tend to use GBPs at doses higher than that recommended, often taking very high doses at once. Although GBPs are most commonly abused orally, they can also be used rectally to increase absorption or administered via injection, inhalation, or smoking after crushing the tablets. To enhance absorption, individuals may also wrap crushed GBP tablets in a pouch, such as toilet paper, before swallowing them.[5]

The euphoric side effect associated with GBP use becomes more pronounced when combined with central nervous system (CNS) depressants, leading to a significant synergistic effect that increases the likelihood of abuse.[14] PGB is absorbed more rapidly than GBP and binds with higher affinity to the α2δ-1 subunit. Therefore, PGB has a greater potential for abuse compared to GBP.[9,15]

Most patients with a history of gabapentinoid abuse have also been found to have a history of other substance abuse.[9,13] The presence of a history of current or past substance abuse as well as psychiatric comorbidity are among the most significant risk factors for developing gapabentinoid abuse. A meta-analysis of case series found that GBP dependence was reported at 1.1% in the general population compared with 22% in drug addiction centers.[16]

It has been reported that GBPs are not fatal, even in overdose unless used in combination with opioids and sedatives.[13] The true addictive potential of GBPs is best reflected by the number of cases in individuals with no prior substance use experience who exhibit signs of behavioral addiction after GBP use, although such cases are rare.[13]

GBP overdose can be fatal, especially when used in combination with opioids and benzodiazepines, and can induce respiratory or cardiac failure.[13] In a study conducted at a French addiction center, 31 deaths related to gabapentinoid use were reported, the majority involving PGB (25 PGB, 6 GBP).[17] Side effects of coma, dyspnea, convulsions, and conduction disorders were observed in nearly all cases related to PGB use.[17] In terms of abuse, PGB rose from 15th place in 2017 to 1st place by 2019.[17] In the study by Grosshans et al.[18] PGB was detected in the urine of opioid-dependent individuals who had no medical indication for its use. Therefore, before prescribing GBP, patients should be carefully evaluated for a history of substance abuse.

Physical symptoms, such as the development of tolerance and withdrawal are more predictive of the recurrence or chronicity of addiction compared to behavioral symptoms like drug-seeking and loss of control.[13] Behavioral addiction symptoms related to GBPs are less frequent than those seen with PGB.[13]

The current high abuse rates of GBPs can be attributed to their broad indications, ease of prescription, rapid dose titration, initial lack of awareness among doctors regarding their abuse potential, the search for alternatives to opioid therapy, relatively low cost, and the ease of illegal acquisition. Most individuals abusing GBPs are men under the age of 40.[19]

the opioid risk tool is commonly used to assess risk during opioid use.[20] A score above 8 on this scale indicates a high risk of opioid addiction.[20] By using this scale on patients before using GBPs, a preliminary idea about their addiction potential can be obtained.

USE OF GABAPENTINOŞDS IN THE TREATMENT OF SUBSTANCE USE DISORDER

The treatment of SUDs involves medications, behavioral therapy, or a combination of both; however, success of the treatment remains limited. Thus, alternative options for withdrawal treatment are still being explored. Although GBPs have addictive potential, they are recommended off-label for the treatment of withdrawal.

GBPs affect the overactive glutamatergic system during withdrawal. It is believed that GBPs alleviate benzodiazepine

(BZD) withdrawal symptoms by reducing glutamate release from glutamatergic nerve terminals and decreasing glutamate binding to the AMPA receptor.[21] Side effects and abuse rates of GBPs are considerably lower than that of BZDs.[21] Although BZDs are an effective short-term treatment for alcohol withdrawal, discontinuing the treatment can lead to life-threatening withdrawal symptoms, and tolerance and addiction can develop even at therapeutic doses.[21] In double-blind, placebo-controlled studies, it has been shown that PGB significantly reduces anxiety scores in patients undergoing BZD withdrawal who were previously treated for generalized anxiety disorder.[22] Although GBPs are recommended off-label for addiction treatment, more randomized controlled trials are needed to substantiate their efficacy.[21]

GABAPENTINOID TOXICITY AND TREATMENT

Even when taken in high doses, these drugs are considered relatively safe when used alone. However, their interaction with other CNS depressants increases the risk of respiratory depression.[14] When taken by themselves, GBPs do not cause significant toxicity.[19] While symptoms like tremors, dizziness, tachycardia, bradycardia, ataxia, and hypotension are generally manageable in outpatient settings, more severe cases may rarely develop mental status changes, coma, or respiratory depression requiring intubation.[19,23]

Cases of PGB toxicity and abuse are increasing day by day, associated with an increase in overall consumption.[19] In PGB toxicity, most patients are also using other substances, especially BZDs, which can intensify clinical symptoms.[19] Isolated GBPs toxicity typically does not present a life-threatening risk.[19]

PGB abuse-related toxicity is more common in men, whereas suicide-related toxicity is more frequent in women.[19]

In cases of GBPs toxicity with tachycardia or hypotension, intravenous hydration should be initiated. Isolated GBPs toxicity shows no benefit from activated charcoal treatment. In cases of respiratory depression, the administration of naloxone is recommended if opioids have been taken concurrently. If myoclonus develops because of GBPs toxicity, it resolves upon discontinuation of the drug. If myoclonus occurs alongside renal failure, hemodialysis should be performed. In renal failure, extracorporeal treatment is suggested along with supportive care. A pharmacokinetic study found that 17%–51% of GBP and >50% of PGB were cleared with 3–4 hours of dialysis.

GABAPENTINOID WITHDRAWAL SYNDROME

Symptoms of GBPs withdrawal syndrome can emerge 12 hours–7 days after discontinuation of the drug, often developing within 24–48 hours.[16] Withdrawal symptoms associated with GBPs include sweating, tachycardia, gastrointestinal symptoms, anxiety, agitation, confusion, catatonia, and epileptic seizures.[16] In a study involving inmates, 85% of those using PGB exhibited withdrawal symptoms, with dissatisfaction and aggression being the most common clinical manifestations.[24]

In the same study, 93% of inmates using PGB were taking it in doses exceeding the recommended maximum dose of 600 mg/day, often in combination with other addictive agents.[24] Gradual reduction of GBPs may alleviate withdrawal syndrome symptoms.[16]

GABAPENTINOIDS AND MORTALITY

GBPs can be prescribed together with opioids for pain management.[25] Because of the stringent controls placed on opioids over the years, off-label medications, including GBPs, have also been prescribed for pain management.[26] The risk of opioid-related mortality increases when used in conjunction with GBPs.[25] While mortality due to overuse of both opioids and GBPs was higher in women until 2020, this difference has since diminished.[26] Opioids slow gastrointestinal motility, which prolongs the retention time of GBPs in the upper small intestine; thus, increasing their absorption and bioavailability.[25] In Australia, between 2000 and 2020, 81.3% of GBPs-related deaths were classified as accidental poisoning, whereas 18.8% were attributed to intentional drug overdose.[14] In GBPs-related deaths, there is a 99.8% prevalence of the use of other non-GBPs medications, frequently including opioids, hypnotics, and antidepressants.[14] Co-contributory diseases in GBPs-related deaths have most commonly been identified as cardiovascular system diseases.[14]

CONSIDERATIONS WHEN PRESCRIBING GABAPENTINOIDS

GBPs are considered a potential safer alternative to opioids, which is why GBPs prescription for chronic pain management is on the rise while the rates of opioid prescriptions are decreasing.[27] However, the potential for side effects increases when GBPs are prescribed alongside opioids.[27]

The most common side effects associated with GBPs are CNS-related symptoms, such as somnolence, dizziness, and walking and balance disorders. However, GABA receptors are not only found in the CNS; they are also present in the gastrointestinal, hematopoietic, and immune systems as well as in the ovaries, bladder, pancreas, lungs, and spleen. Although stroke and malignancy have been reported in users of GBPs, there is insufficient data to associate these with the medication.[27]

CONCLUSION

Given the increased usage in recent years, applying opioid risk tools to each patient before starting treatment can provide preliminary insights into the potential for addiction prior to prescribing GBPs. Moreover, avoiding the drug's prescription to those scoring 8 or above on the scale may help prevent the development of GBPs-related addiction.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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