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Medical and Psychiatric Comorbidity in Patients with Pregabalin Abuse: Review Article

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ABSTRACT

Background: Anxiety, sadness, personality disorders, and suicide are just some of the common psychiatric conditions that often co-occur with pregabalin addiction. Pregabalin (PGB) is one of many psychoactive prescription medications that has seen a rise in its off-label use in recent years. Multiple drug users and patients in methadone treatment programs have been found to take PGB at high quantities to enhance the effects of methadone, alleviate withdrawal symptoms, or both. This is why high-risk populations need precise toxicological monitoring.

Objective: This review article aimed to study prevalence of medical and psychiatric comorbidity in patients with pregabalin Abuse.

Methods: Medical, psychiatric comorbidity and the pregabalin abuse were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from March 2008 to January 2022 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusions: Pregabalin abuse was associated with medical illnesses such as neuropathy and epilepsy and psychiatric disorders such as anxiety and depression.

Keywords: Medical, Psychiatric, Comorbidity, Pregabalin abuse.

INTRODUCTION

Addiction or substance use disorder is described by a constellation of physical, mental, and behavioral symptoms that arise when substance use persists despite obvious risks. As a result of drug overuse and usage, this may occur [(1)].

Pregabalin is a d2-serotonin-like molecule that is structurally related to gabapentin, a chemical that mimics the mammalian neurotransmitter gamma-aminobutyric acid. As inhibitory modulators of neuronal excitability, they dampen the overexcited neurons' activity while leaving the normally active ones alone [(2)]. Accepted daily dosages of pregabalin range from 150 to 600 mg, making it a useful therapy option for a variety of conditions including fibromyalgia, generalised anxiety disorder, peripheral neuropathic pain, and partial epilepsy. In 2005, the United States government placed pregabalin in schedule V of the Controlled Substances Act (CSA) [(3)]. For whatever reason, men are more likely to suffer from pregabalin abuse problem than women. Underage users of pregabalin are more common than those of legal drinking age. Pregabalin abuse typically occurs for the following reasons: to have a good night's rest; to treat one's own anxiety, peer pressure, or despair; and to enhance one's mood [(4)].

There may be more to the problem than just pregabalin and gabapentin abuse for their euphoric effects. Suicidal thoughts and depression have also been linked to pregabalin use. Ten percent of patients in one case series who had just begun therapy with pregabalin reported mood disturbances, including depression or suicidal ideation, or both, which resolved after medication was stopped or the dose was lowered. Deaths could be prevented by keeping an eye out for signs of depression after therapy has begun and dosage has been increased. Pregabalin has just been added to Egypt's schedule of prohibited substances due to the country's rising usage rate [(5)].

An increasing number of people are misusing prescription drugs for recreational purposes, which is a major public health issue. Prescription psychotherapy medicines were the second most commonly used illegal drug category among all age groups in the United States in 2015, behind only cannabis. European countries showed comparable data. [(6)].

Prescription sedatives and hypnotics are frequently abused. Barbiturates, benzodiazepines (BZDs), and BZD-like pharmaceuticals (z-hypnotics), opioids and opioid substitution treatments (for pain management), and stimulants (for ADD/ADHD) are all examples (ADHD). It's not just stimulants like methylphenidate that people abuse, but also antidepressants, Parkinson's pharmaceuticals, cold and cough remedies, and more [(7, 8)].

EPIDEMIOLOGY

Pregabalin is a prescription drug that has psychoactive effects and is used for a variety of medical conditions. Lyrica is the brand name under which it was first sold in the United States and the European Union (Pfizer, NY, USA). In the European Union (-EU-), pregabalin has been approved for use in the treatment of epilepsy, neuropathic pain, and generalized anxiety disorder. When it comes for treating fibromyalgia, pregabalin was the very first drug to receive FDA approval [(9)].

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In the US, pregabalin can be prescribed for the treatment of fibromyalgia, epilepsy (partial-onset seizures), postherpetic neuralgia, and diabetic neuropathy [10]. Pregabalin's normal therapeutic dose is 150–600 mg daily, split into two or three doses. In 2011, pregabalin was one of the top 30 most commonly prescribed drugs in the United States [11].

When people who had been using pregabalin died, the medication was found at quantities varying from 0.4 to 17 mg/L (median 5.6 mg/L) in their femoral blood and from 1.5 to 11 mg/L (median 4.6 mg/L) in their cardiac blood. Off-label uses for the drug include treating bipolar disorder, alcohol/narcotic withdrawal, ADHD, restless legs syndrome, trigeminal neuralgia, and non-neuropathic pain syndromes, among others [12].

About one-third of approved applications for drug reimbursement in Norway were for pregabalin, according to an analysis by **Spence** [13], who looked at trends in drug reimbursement spending on potentially addictive medicines in patients with severe/nonmalignant chronic pain from 2008 to 2011. Anecdotal evidence suggests a growing illicit market for gabapentinoids, with some forms being available online without a doctor's prescription [14].

Deaths linked to pregabalin have steadily increased since the drug first showed up in UK mortality records in 2006. The United States, France, and Finland, among others, have come to similar conclusions. There is sufficient evidence of misuse potential to place pregabalin in Schedule V. (albeit less potential than Schedule IV, III, and II drugs) [15].

The Egyptian Minister of Health has placed pregabalin on schedule III. At least two factors necessitated its planning. Patients taking pregabalin were more likely than those taking a placebo (N=5500 total) to report experiencing euphoric feelings (4% versus 1%, respectively) [16].

MEDICAL AND PSYCHIATRIC COMORBIDITIES

Gabapentin and pregabalin are the two drugs that make up the gabapentinoids. In the United States, gabapentin is approved for use in treating focal seizures and post-herpetic neuralgia, whereas in the United Kingdom, it is approved for use in treating peripheral neuropathic pain as well as focal seizures [17].

Pregabalin is prescribed for similar reasons, in addition to fibromyalgia and generalized anxiety disorder (GAD). Because of their widespread success since their first release in 1993, these pharmaceuticals are now among the most frequently prescribed medicines overall, with many of those prescriptions likely being made for unapproved uses. Prescriptions for gabapentin were found to be 95% off-label in a small sample of 105 Medicaid patients, with at least 10% being for psychiatric illnesses [18].

In the United Kingdom, at least fifty percent of gabapentinoid prescriptions are non-approved uses, and twenty percent of them are administered alongside opioids [19]. According to data collected from the TriNetX electronic health records network in the United States, Some 13.6% of those diagnosed with bipolar disorder (BD), 11.5% of those diagnosed with anxiety disorders, and 12.7% of those struggling with sleeplessness have been prescribed gabapentin at some point [20].

Though gabapentin is commonly used off-label to treat BD, there is little proof of its effectiveness. Meta-analysis of pharmacologic treatments for acute mania found that gabapentin did not outperform placebo in improving patient outcomes [21].

Systematic evaluations of gabapentin treatment for mental and/or drug use disorders have indicated mixed results, with inconclusive evidence of benefit in BD but maybe of efficacy for other anxiety disorders. No new investigations with pregabalin were conducted, no attempt was made at a quantitative synthesis, and only studies that had already been published were considered [20-22].

Pregabalin has been used for the treatment of a wide variety of anxiety disorders and acute anxiety states, including post-traumatic stress disorder (PTSD) and preoperative jitters. Pregabalin has been shown to be effective in treating generalized anxiety disorder (GAD), but its usefulness in treating other forms of anxiety, such as social anxiety disorder (SAD), is less evident [23].

The authors of a recent study on pregabalin for perioperative anxiety did not try to synthesize the available data quantitatively. Again, the information is hazy on whether or not gabapentinoids help with insomnia treatment [24].

As a whole, these investigations demonstrate that the efficacy of gabapentinoids in a number of these illnesses is not well supported by the available data. In addition, there is evidence of misuse and addiction risk, hence the UK government has reclassified these substances as controlled substances for 2019. Because of its higher potential for dependency and misuse, pregabalin (unlike gabapentin) has been a federally regulated substance in the United States ever since it hit the market [25].

Given their route of action, gabapentinoids are promising candidate compounds for psychiatric disorders. Despite the name, they function largely by binding to the 2 auxiliary subunit, which modulates channel trafficking and function, and so suppressing neuronal voltage-gated calcium channel (VGCC) currents [26].

In BD, Very few randomized controlled trials (RCTs) have been conducted to determine the efficacy of gabapentinoids, and the scarcity of research on pregabalin emphasizes this point. Due to differences in study populations, methods, and outcomes, a quantitative synthesis could not be conducted. However, there is insufficient data to recommend the use of gabapentinoids for the treatment of BD as they are currently being administered [27]. It is likely that the widespread effectiveness of gabapentinoids across the anxiety spectrum reflects a pharmacologic influence on

trans-diagnostic anxiety phenotypes mediated by 2-dependent pathways. Most people with BD also suffer from anxiety, which may be due to a hereditary susceptibility. In addition, it's linked to more severe symptoms and a variety of unfavourable clinical outcomes. However, no clinical trials have yet examined the effectiveness of gabapentinoids in the treatment of anxiety in BD. Future studies could focus on the use of gabapentinoids or modified 2 ligands for the selective treatment of 'bipolar anxiety' [(28)].

Recent Egyptian research [(29)] found that 47% of the sample suffered from generalised anxiety disorder, 74% from major depressive disorder (with some patients suffering from both disorders), 78% from borderline personality disorder (with some patients also suffering from antisocial personality disorder), and 37% from both. Subjects with serious depression, generalized anxiety, a history of suicide ideation or behavior, or borderline personality disorder showed a statistically significant increase in suicidal ideas.

Similarly, another study indicated that the vast majority of pregabalin users (86.7%) used the drug on a daily basis. Among these individuals, over 79% misused both pregabalin and another substance, the most common additional drugs were tramadol (67.4%), heroin (66.3%), cannabis (65.1%), other drugs (44.6%), and benzodiazepines (27.7%). Sixty-two point seven percent of people tested positive for drugs in their urine during the screening process; the most common positives were for heroin (41%) and cannabis (34.9%). Only 32.6% of the participants showed suicidal ideation, the remaining 67.4% did not. Of those at risk for suicide, 19.3% were at low risk and 13.3% were at high risk. Suicide risk was significantly elevated among individuals with a positive urine test for pregabalin who were also misusing the drug on a chronic basis. The length of time pregabalin was abused for, the highest amount taken, and the amount used daily were all positively correlated with the Beck Suicidal Ideation score. Suicidal ideation was also positively correlated with both the dose and duration of tramadol misuse, suggesting a causal relationship between the two [(30)].

It was found by **Abelghani *et al.*** [(31)] that almost 50% of patients abusing pregabalin had some form of cognitive impairment. Patients who abused pregabalin were more likely to have impairments in delayed recollection (OR = 3.0, 95% CI = 1.5-7.9), orientation (OR = 2.60, 95% CI = 1.2-4.9), and total Montreal Cognitive Assessment scores than control subjects (OR: 2.6, 95 percent CI: 1.7-9.8). Abuse of pregabalin has been linked to deficits in naming, language, and abstraction across a range of patient populations.

CONCLUSIONS

This study showed that off-label use of gabapentinoids in the treatment of mental health problems is not supported by substantial data, with the exception of a few anxiety states. Therefore, caution is warranted, and more evidence of efficacy and safety is necessary, despite the allure of the genetic and pharmacological justification for their usage. The therapeutic profile of modified 2 ligands, targeting certain subtypes or isoforms, may also be improved. Dependence on pregabalin is strongly correlated with diagnosable cases of major depressive disorder, anxiety, borderline personality disorder, and antisocial personality disorder. A number of mental disorders have been linked to increased suicide ideation. Pregabalin, like other narcotics of abuse, should only be used cautiously and under medical supervision.

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