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Systematic Review

Seizures as an Adverse Effect of Pregabalin Consumption: A Systematic Review

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Abstract

Background: Pregabalin (PGB), a gabapantinoid drug, which is commonly prescribed by physicians and some patients abuse it, can lead to seizure. Pregabalin-induced seizures (PGBIS) and their risk factors were systematically reviewed.

Methods: The databases were searched from January 1, 2011, to August 1, 2022. Studies that reported PGBIS were included. The records were assessed according to the PRISMA-P protocol.

Findings: From a total of 224 records, 11 studies were included, comprising four cross-sectional studies and seven case reports. The data from the cross-sectional studies were notably limited. Seven studies documented nine cases (five females and four males), with a median age of 51 years (ranging from 16 to 65). PGB was used for therapeutic purposes, abuse, and suicide attempts. One case had kidney dysfunction. A significant number of cases used PGB with other drugs. There was no difference between the ingested dose of PGB in men (2700 and 4200 mg) and women (3000, 1200, 3825, and 1200 mg). All cases had normal renal function, except for one case.

Conclusion: PGBIS is not common. However, it was reported for all purposes of PGB consumption. No specific risk factor for PGBIS was found. It was more commonly reported in females, patients who consumed high doses of PGB (>1200 mg), patients who ingested multiple drugs, and patients with renal insufficiency. The dosages used for therapeutic purposes were much lower than in the other two groups.

Keywords: Pregabalin, Seizures, Neurotoxicity syndrome, Adverse effect

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Introduction

Pregabalin (PGB), chemically known as (S)-3-(aminomethyl)-5-methylhexanoic acid, is an antiepileptic medication that functions by attaching to the alpha-2-delta subunit of voltage-gated calcium (Ca^{2+}) channels, thereby producing its anticonvulsant effects.[1,2] The important attributes of PGB include rapid absorption with high bioavailability, blood-brain barrier (BBB) crossing, long half-life (about 6.3 hours), and low metabolization.[3] PGB is commonly prescribed for managing seizures, post-herpetic neuralgia, migraines, fibromyalgia, and neuropathic pain.[4,5] Addiction and abuse of PGB have increased recently in different countries, hence, this is becoming a health concern.[6] In Europe (Southern Europe, Scandinavian countries, and Germany), many of the deaths after PGB consumption were associated with drug abuse.[7-10] The first documented instance of PGB being used recreationally occurred in 2011, which garnered significant attention from the French Addictovigilance Network (FAN).[11] Several neurological side effects following PGB abuse have been reported, including seizures, encephalopathy, cognitive impairment, coma, confusion, psychosis, dizziness, CNS depression, somnolence, and ataxia.[12-15] Tachycardia, tremors, anxiety, diaphoresis, diarrhea, and auditory hallucinations have also been reported by the World Health Organization

(WHO).[16] Seizure, as a complication of PGB intoxication in an antiepileptic drug poisoning, is noticeable. We aim to present a comprehensive systematic literature review on PGBIS and provide clinicians with an evidence-based framework to recognize PGBIS.

Methods

This systematic review protocol was developed following the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17]

Search strategy

Under the direction of a biomedical librarian, we searched Science Direct, MEDLINE/PubMed, Google Scholar, Scopus, and Web of Science databases for studies conducted between January 1, 2011, and August 1, 2022, using the search terms. This time frame was chosen because the number of studies reporting PGB's adverse effects increased significantly after 2011.[6] The following combination of keywords, including "pregabalin," "toxicity," "drug overdose," "seizure," "convulsion," and "poisoning," were used, in combination with the Boolean operators "AND" to intersect different concepts and "OR" to encompass similar concepts (Table 1). In addition, MeSH terms within PubMed were used to augment our search.

Inclusion and quality criteria

Studies were included if they evaluated PGB specifically and reported its neurologic adverse effects, including seizures, and were published in journals as case reports, cross-sectional studies, or abstracts of congress papers. Articles were excluded if they did not match the search strategy or were not published in English journals.

Screening process and data extraction

Articles were imported into the EndNote database, and duplicate records were removed. Two experienced authors extracted data sets regarding exclusion or inclusion criteria. A thorough discussion involving a third reviewer was held in case of disagreement until a consensus was reached. All abstracts and full-text articles were examined to determine eligibility via a systematic search of the above-mentioned database. This systematic review study did not assess the risk of bias due to limited reporting and the complexity of studies.

Table 1. PubMed search query

Search query
(((((((toxicity [Title/Abstract]) OR (intoxication[Title/abstract])) OR (overdose[title/abstract])) OR (overdoses[title/abstract])) OR (poisoning[title/abstract])) OR ((("toxicity" [subheading]) OR "drug overdose"[mesh]) OR ("poisoning"[mesh] OR "poisoning" [subheading])))
AND
(((((((((seizure[title/abstract]) OR (seizures[title/abstract])) OR (convulsion[title/abstract])) OR ("seizures"[mesh])
AND
(((pregabalin[title/abstract]) OR (lyrica[title/abstract])) OR ("pregabalin"[mesh]))
AND
(2011:2022[pdat])

Data synthesis

The requisite information obtained from each eligible study that met the inclusion criteria, including the research paper title, authors' names, date of publication, study site, publication type, number of subjects, PGB-induced seizure, any detail of PGB-induced seizure cases, the suggested risk factor(s) for convulsion, prevalence of seizures, and other used drugs, were extracted from the articles.

Results

Figure 1 illustrates the flowchart depicting the study selection process according to the PRISMA guidelines. All databases were reviewed until August 1, 2022, and 224 records were retrieved. After removing 27 duplicates, 197 articles were identified, and 11 studies were included: four cross-sectional studies (Table 2) and seven case report studies (including nine cases, Table 3).

The association between PGB use and seizures was found in four cross-sectional studies, including 20 patients. Some cross-sectional studies indicated PGB abusers or intoxicated PGB users. Thus, the details of PGB-induced seizures were not reported. These cases were treated with 200–4000 mg/kg of PBG.[11,18,19,21,23,28] Most of the PGB-intoxicated patients were male.[18,28] However, the exact gender and age of PGBIS cases were not reported. During follow-up, two cases of seizures lasting 90–120 seconds were reported.[23,28]

Isoardi et al[18] reported 488 PGB intoxication presentations in 413 patients over five years. Among the 488 PGB presentations, 59 presentations (58 cases) ingested only PGB, 341 presentations (299 cases) ingested multiple drugs, and 121 presentations (108 cases) were recreational PGB users. Seizures were observed in 10 (2%) patients, three cases (5%) of isolated PGB-intoxicated cases, five cases (1%) of multi-drug-poisoned cases, and four cases (3%) of recreational PGB abusers. The doses of PGB associated with seizure occurrences were 600 mg, 900 mg, and 1800 mg. Notably, one patient who took 600 mg had a prior history of seizure disorder. All seizures were self-limiting, lasting about one minute, and with no instances of status epilepticus reported.[18]

In another report by Dufayet et al,[19] 1188 cases of adults and 382 adolescents who experienced acute intentional exposure to PGB were enrolled. Their data were compiled from the French National Database of Poisonings (FNDP) between 2004 and 2020. However, the authors did not report the adult findings. A total of 94 out of 382 adolescent cases (24.6%) were recreational

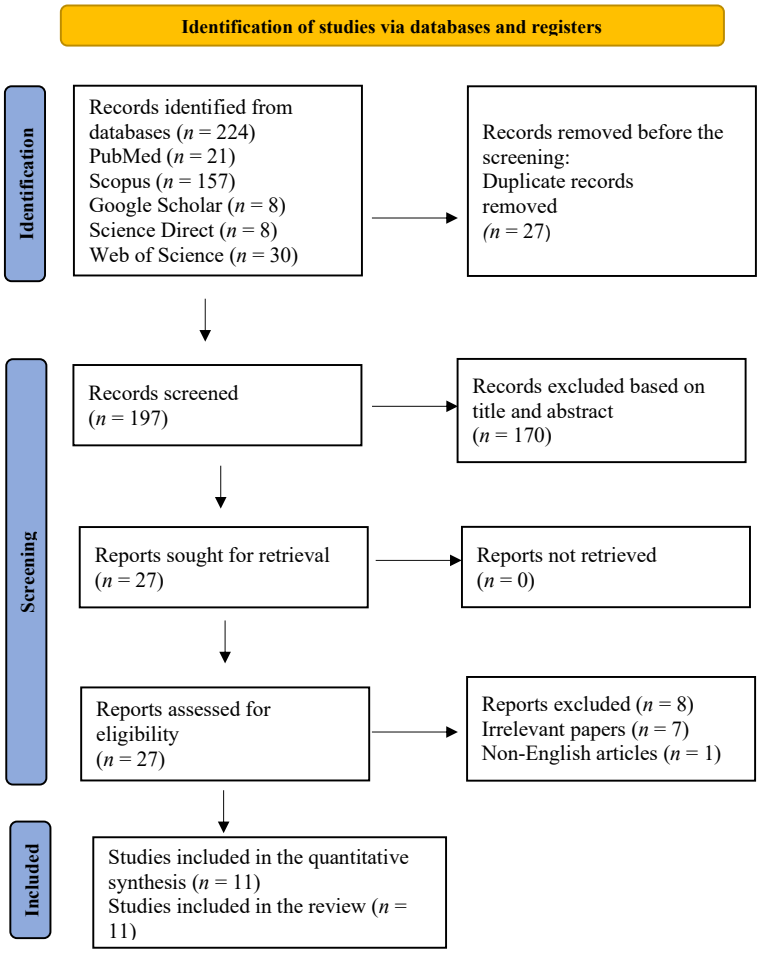

Figure 1. Flow chart of the study selection process according to the PRISMA guidelines

Table 2. The summarized cross-sectional studies that reported pregabalin (PGB)-induced seizure

Authors (year) (reference)	Cases	Seizure / sample size	Gender #	Median of age (years) #	Dose of PGB	Risk factors	Other
Isoardi (2020)[18]	All cases	10/488	57% male	41	Median = 1200 mg		
	PGB only intoxicated	3/58	71% male	39	600 mg 900 mg 1800 mg	pre-existing seizure disorder in one case (600 mg)	All cases were self-limiting and lasted around one minute
	recreational PGB abusers	4/121	81% male	36	Median = 900 mg		
Dufayet (2021)[19]	All cases (recreational PGB abusers and suicidal attempts)	2/382	5.3/1 male/ female	15	NR	NR	Only adolescents were reported
Ryan (2016)[20]		1/56	54% male	44	Unknown	NR	The patient had a history of seizures and experienced two episodes of seizure
Tambon (2021)[11]	PGB in co-consumption	6/185	72.5% male	24		Co-consumption drugs	
	PGB alone, recreational abuse	1/73	Female ##	15 ##	1200 mg ##	NR	

#The age and male/female ratio were not reported for PGB-induced seizure cases. The summarized items belong to all samples of the study.
The summarized data belongs to the case.

PGB abusers, and others had suicidal attempts. Mild to moderate neurological symptoms such as drowsiness and ataxia were reported in 54% and 27% of the adolescents, respectively. Only eight cases of adolescents (five of them ingested PGB alone) presented severe symptoms such as coma (Glasgow coma scale < 7, five cases) or generalized seizures (two out of eight cases).[19]

One conference presentation reported that among 56 (54% male) PGB overdose cases with a median age of 44 years (ranging between 18 and 67), only one patient had two seizures after PGB overdose at an unknown dose. The patient had a history of seizures.[20]

Table 3. The summarized case reports of the pregabalin (PGB)-induced seizure

Authors (year) (reference)	Single or multiple drug intoxication	Age (years)	Gender	Dose (mg)	Other drugs	Manner	Other
Ocak (2019)[21]	Single	23	Male	4200	-	Suicide attempt	GTC lasted for two minutes and was stopped by diazepam
Hussain (2019)[22]	Single	65	Male	75 mg daily for a few days	-	Therapeutic use	History of DM, HTN, and CKD on regular hemodialysis/ absence status
Slocum (2018)[23]	Single	54	Female	3825	-	Intentional overdose	
Reedy (2010)[24]	Single	16	Male	2700 mg ingested and insufflated	-	Intentional overdose	GTC one hour later
Reedy (2010)[24]	Single	17	Male	Ingested and insufflated	-	Intentional overdose	One self-limited and one treatment-limited episode of GTC
Hsiao(2022)[25]	Multiple	51	Female	1200 and 1000	Multi-drug abuser and antiviral drug	Drug abuse	PRES
Ozturk (2019)[26]	Single	23	Female	3000–4500 mg by nasal inhalation		Drug abuse	
Haji (2021) [27]	Multiple	51	Female	300 mg BID	Tapentadol	Therapeutic use	
Haji (2021) [27]	Multiple	54	Female	75 mg BID one year	Tapentadol, aspirin, propranolol, duloxetine, amitriptyline, frusemide, and eletriptan	Therapeutic use	

GTC, generalized tonic-clonic seizure; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; PRES, posterior reversible encephalopathy syndrome.

Seizures were observed in seven patients, including a 15-year-old girl who experienced seizures after consuming 1200 mg of PGB despite having no previous epilepsy history. Other patients who suffered seizures had co-ingestions of other drugs.[11]

We also found seven case reports that reported nine cases of PGB-induced seizures (Table 3). These case reports included five women and four men. Three cases used PGB for therapeutic purposes, two for abuse, and four for suicide. The dosage consumed by patients who used the drug for therapeutic purposes was much lower than other groups. In one case, a 23-year-old man attempted suicide by ingesting 4200 mg of PGB. He was conscious with normal vital signs. He suddenly lapsed into a generalized tonic-clonic (GTC) seizure that lasted for about two minutes and was stopped by diazepam. Then, he had metabolic acidosis and became unconscious after the seizure. After three hours of hemodialysis, the metabolic acidosis and loss of consciousness were resolved.[21]

Another case involved a 65-year-old male with a medical history of diabetes mellitus, hypertension, and chronic kidney disease who was undergoing regular hemodialysis. He used 75 mg of PGB daily for diabetic polyneuropathy. He was brought to the emergency department after being confused for 24 hours. An urgent EEG revealed an absence status. He was treated with lorazepam and valproate.[22]

Reedy and Schwartz reported two cases of PGBIS in 2010. The first individual was a 16-year-old boy who suffered from GTC one hour after ingesting and insufflating 2700 mg of PGB to get high. The second case was a 17-year-old boy who ingested and insufflated an unknown amount of PGB. He had two GTC seizures. The first one was self-limited, and the second needed treatment.[24]

Hsiao et al. reported posterior reversible encephalopathy syndrome (PRES) in a 51-year-old female multi-drug abuser who was schizoaffective and had a human immunodeficiency virus infection. She used methadone and antiretroviral drugs and had a history of benzodiazepine and other prescription drug abuse. She was hospitalized twice in three days following consumption of 1200 mg and 1000 mg of PGB, respectively. The authors did not report obvious seizure attacks. They reported that she had PRES based on her clinical manifestations and imaging findings. Seizure was one of the main features of PRES.[25]

Additionally, Haji et al reported that two elderly females who used PGB for therapeutic purposes were admitted with loss of consciousness. Their EEGs showed epileptiform activity, and they were diagnosed with encephalopathy. They had no history of obvious seizures and showed only epileptiform activities on their EEG.[27]

We could not find any specific risk factors or features in PGB-induced seizures. However, renal insufficiency may be an influential underlying condition. In cases that reported gender, the female/male ratio was 6/4. It is noticeable that four of the six females were over 50 years old. Except for two of them that had no apparent seizures, others used more than 1200 mg PGB. Except for one man on regular hemodialysis, the other men ingested high doses (> 2000 mg) of PGB. There was no difference between the ingested doses of men (2700 and 4200 mg) and women (3000, 1200, 3825, and 1200 mg) in patients with normal renal function and single-drug poisoning.

Discussion

In this article, we reviewed the effect of PGB-induced

seizures in several cases. PGB as an anticonvulsant drug[28] may aggravate myoclonus and myoclonic seizures in people with progressive myoclonic epilepsy type 1.[29] From a mechanistic view, it acts on alpha-2-delta sites of voltage-dependent calcium (Ca^{2+}) channels.[1,2] The upsurge of oxidative stress, deregulating neurotransmitter release, antioxidant depletion, and evoking brain tissue inflammation and apoptotic mediators are thought to be related to the pathophysiology of PGB-induced neurotoxicity.[30] Administration of a high dose of PGB in animal models disrupts p38 mitogen-activated protein kinase (p38-MAPK) signaling.[31] Disruption of p38-MAPK-mediated signaling promotes temporal lobe epilepsy and induces neuronal hyperexcitability.[32-34] Dysregulation of the c-Jun N-terminal kinase (JNK) pathways may also be responsible for PGB-induced neurotoxicity.[31,32,34,35]

Acute or chronic toxicity of PGB induces encephalopathy,[25,27] which can cause obvious seizures or epileptiform activity. There is evidence that PGB is associated with constant triphasic waves (TWs) and slow background activity,[36] which are characteristics of toxic metabolic encephalopathy.[37]

In the current review, almost none of the authors of the selected case reports detailed their cases' seizures. It is assumed that the reports of seizure attack events were based on the observations of people around the patients, not those of medical staff. We found a few reports of seizures in hospitalized people. Thus, it is possible that some of the recorded seizure attacks were false and associated with other temporary neurological complications of PGB, such as myoclonus or negative myoclonus.[38] However, the EEG findings of epilepsy were reported in three cases who suffered from encephalopathy.[24,27] Myoclonus or negative myoclonus are known as reversible PGB side effects.[38] According to evidence, induction of negative myoclonus by PGB may happen in patients who receive therapeutic doses or in patients with normal kidney function.[38] PGB-induced myoclonus is characterized by signs such as sudden jerks, shakes, or spasms localized to one part of the body or all over the body.[25,39] Due to its "seizure-like" nature, physicians might interpret this adverse drug reaction as a true seizure, leading to unnecessary and aggressive management.[40]

PGB can cause serotonin syndrome, especially when it is combined with other serotoninergic agents.[41] Additionally, in the systematic review of PGB-associated movement disorders, myoclonus was observed in 12.7% of cases (39/305 cases).[42]

In contrast to gabapentin, the oral bioavailability of PGB does not drop at high doses. Hence, more than 90% of the ingested drug is absorbed rapidly through the gastrointestinal tract. The maximum plasma concentrations of PGB are achieved in one hour, which is sufficient to induce neurotoxicity.[43] PGB is not subject to metabolic processes and is excreted via the kidneys with an elimination half-life of approximately six hours. Its clearance rate is directly proportional to creatinine clearance, and a decrease in glomerular filtration rate (GFR) can lead to an accumulation of PGB in the serum, significantly contributing to its toxicity.[44,45] We could not find the values of renal function tests for PGB-induced seizure cases, thus, in this review, we suggest that kidney function was not associated with PGBIS.

Furthermore, food and drugs have minimal effect on the absorption and pharmacokinetics of PGB[3]. According to studies, some serotonergic drugs, caffeine, and tapentadol[27,41,46] may change PGB pharmacokinetics and lead to a seizure.

According to the collected case reports in the present review, the number of females with PGB-induced seizures was higher than that of men. In addition, except for a lower volume of distribution in women in comparison to men, no gender variation in the pharmacokinetics of PGB has been observed[47] even though generally, the seizure threshold in females is lower than in men.[14,48] Estrogen is recognized for its potential to increase seizure risk, while progesterone tends to have a suppressive effect. Additionally, estrogen's activity diminishes the inhibitory effect on gamma-aminobutyric acid (GABA-A) receptors, enhances glutamate receptor excitation, and promotes excitatory synaptic activity in neurons. However, the majority of PGB-induced seizures were observed in cases that were over 50 years old and were at the menopause stage, which means they had low estrogen levels. About two-thirds of females with PGB-induced seizures were older than 50 years old. However, in the elimination of PGB, renal function plays a more critical role in comparison to other factors, such as age or gender.[3] According to Semel et al, the relative risks for PGB-induced adverse drug reactions had a positive correlation with PGB dose, while no correlation was found with age.[49]

Conclusion

Seizure is an uncommon complication of PGB. Seizures were reported in patients who used PGB for any purpose (therapeutic, abuse, or suicidal attempt). Although we could not find a specific risk factor for PGB-induced seizures, they were more commonly reported in females, patients who took high doses of PGB (>1200 mg), patients who ingested other drugs such as tapentadol concomitantly, and patients with renal insufficiency within therapeutic range. The dosages taken by patients who used the drug for therapeutic purposes were much lower than the other two groups. More detailed studies are needed to determine the risk factors for PGB-induced seizures.

Authors' Contribution

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Writing-original draft: Zahra Oskouei, Amene Raouf-Rahmati, Hamid Jomehpour.
Writing-review & editing: Mohammad Moshiri, Leila Etemad.

Competing Interests
No conflicts of interest have been reported.

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Not applicable.

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