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Seizures as adverse events of pregabalin consumption: A systematic review

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Abstract

Objectives:

Pregabalin (PGB)-induced seizures (PGBIS) and their risk factors was systematically reviewed.

Methods:

The databases were searched from January 1, 2011 to August 1, 2022. Studies were included if they reported PGBIS. The recorded were assessed according PRISMA-P protocol.

Results:

Out of 224 records, 11 papers (4 cross-sectional studies and 7 case reports) were included. The cross-sectional studies reported very limited data. 9 cases (5 women and 4 men) with a median age of 51 years (16-65) were reported in 7 studies. 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). Except one case, all cases had normal renal function.

Conclusions:

PGBIS is not common. but reported in all purpose of PGB consumption. None specific risk factor for PGBIS 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

1. Objectives

Pregabalin (PGB), (S)-3-(aminomethyl)-5-methyl hexanoic acid, as one of the antiepileptic drugs, acts via binding to the alpha2-delta site of voltage-dependent calcium (Ca^{2+}) channels to exert its anticonvulsant activity (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 widely used for the treatment of seizures, post-herpetic neuralgia, migraine, fibromyalgia, and neuropathic pain (4, 5). Addiction and abuse of PGB has 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). In addition, the first case report of the recreational use of PGB was observed in 2011 and received high 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 (12-14). Tachycardia, tremors, anxiety, diaphoresis, diarrhea, and auditory hallucinations have also been reported by the World Health Organization (WHO) (15). Seizure, as a complication of PGB intoxication, in an antiepileptic drug poisoning is noticeable. Our objective is to present a comprehensive systematic literature review related to PGBIS and to provide clinicians with an evidence-based framework in which to recognize PGBIS.

2. Method

This systematic review protocol was completed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16).

2.1. 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 from January 1, 2011 to August 1, 2022 using the search terms. This time duration was chosen because after 2011 the number of studies reporting Pregabalin adverse effects enhanced significantly (6). The following combination of keywords with the recruitment of the Boolean operator “AND” to intersect different concepts and “OR” to encompass similar concepts including "Pregabalin," "toxicity," "drug overdose," "seizure," "convulsion," "poisoning," (Table,1). In addition, MeSH terms within PubMed were used to augment our quest for enlightenment.

2.2. Inclusion and quality criteria

Studies were included if they evaluated PGB specifically and reported its neurologic adverse effects including seizures published in journals as case report, cross sectional or abstract of congress. Articles were excluded if manuscripts were not matched with the search strategy or were not published in English language journals.

2.3. Screening process and Data extraction

Articles were imported into the EndNote database and duplicate records were removed. Data sets regard to exclusion or inclusion were extracted by 2 experienced authors. In cases with no agreement, a thorough discussion involving a third reviewer was held until reaching a consensus. All abstracts and full-text articles were examined to determine eligibility via a systematic search of the above-mentioned database. Risk of bias was not assessed in this systematic review study due to limited reporting and complexity of studies.

2.4.Data Synthesis

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

3. Results

The flow chart of the study selection process based on PRISMA is presented in Fig. 1. All databases until August 1, 2022 were reviewed and 224 records were retrieved. After removing 27 duplicates, 197 articles were identified in which 11 studies were included: 4 studies were cross-sectional (table 2) and 7 studies were case reports (including 9 cases, table 3).

The association between PGB use and seizures was found in 4 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, 17-21). Most of the PGB-intoxicated patients were male (19, 20). But the exact gender and age of PGBIS cases were not reported. During follow-up, 2 cases of seizures lasting 90-120 seconds were reported (17, 19).

Isoardi, *et al* (20), reported 488 PGB intoxications presentations in 413 patients over 5 years. Among the 488 PGB presentations, 59 presentations (58 cases) ingested only PGB and 341 presentations (299 cases) ingested multiple drugs and 121 presentations (108 cases) were recreational PGB user. Seizures were observed in 10 (2%) of all of patients, 3 cases (5%) of isolated PGB intoxicated cases, 5 cases (1%) of multi-drug poisoned cases and 4 cases (3%) of recreational PGB abusers. The doses of PGB that promoted seizures were 600 mg, 900 mg, and 1800 mg. Of these cases, one patient who ingested 600 mg of PGB had a pre-existing seizure disorder. All seizures were self-limiting and lasted approximately 1 minute. No status epilepticus was reported (20).

In another report by Dufayet *et al* (18), 1188 cases of adults and 382 adolescents who experienced acute intentional exposure to PGB were enrolled. Their data was compiled from the French National Database of Poisonings (FNDP) between 2004 and 2020. However, the authors did not report adult findings. 94 of 382 adolescent cases (24.6%) were recreational PGB abusers and others had suicidal attempts. Mild to moderate neurological symptoms such

as drowsiness and ataxia were reported in 54% and 27% of adolescents, respectively. Only 8 cases of adolescents (5 of them ingested PGB alone) presented severe symptoms such as coma (Glasgow coma scale < 7) in 5 cases, or generalized seizures (2 of 8 cases) (18).

One conference presentation reported that among 56 (54% male) PGB overdose cases with a median age of 44 years (range: 18-67) only 1 patient had two seizures after PGB overdose at an unknown dose. The patient had a past history of seizures (19).

Of a total of 258 individuals who abused PGB, seizures were reported in 7 patients. Among these patients, seizures occurred in a 15-year-old girl without any history of epilepsy after an intake of 1200 mg. Other patients who suffered seizures had co-ingestions of other drugs (11). We also found 7 case reports that reported 9 cases of PGB-induced seizures (Table 3). Case reports included 5 women and 4 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 in the 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 2 minutes and was stopped by diazepam. Then, he had metabolic acidosis and became unconscious after the seizure. After 3 hours of hemodialysis, the metabolic acidosis and loss of consciousness were resolved (21).

Another case was a 65-year-old man with a history of diabetes mellitus, hypertension, and chronic kidney disease on regular hemodialysis. He used 75 mg PGB daily for diabetic polyneuropathy. He presented 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 case involved a 16-year-old boy who experienced 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 snorted an unknown amount

of PGB. He developed two GTC seizures. The first one was self-limited and the second needed treatment (23).

Hsiao *et al* reported Posterior Reversible Encephalopathy Syndrome (PRES) in a 51-year-old multi-drug abuser woman who was schizoaffective and had a human immunodeficiency virus infection. She received methadone and antiretroviral drugs and had a history of benzodiazepines 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 her imaging findings. Seizure was one of the main features of PRES (24).

Additionally, Haji *et al.* reported 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 (25).

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 defined gender, the female/male ratio was 6/4. It is noticeable that 4 of 6 females were over 50 years old. Except for two of them that had no obvious seizure, 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 intoxication.

4. Discussion

In this article, we reviewed the effect of PGB-induced seizures in several cases. PGB as an anticonvulsant drug (26) may aggravate myoclonus and myoclonic seizures in people with Progressive Myoclonic Epilepsy Type 1 (27). From a mechanistic view, it acts on alpha2-delta sites of voltage-dependent calcium (Ca^{2+}) channels (1, 2). Upsurge of oxidative stress,

deregulating neurotransmitters release, antioxidant depletion, and evoking brain tissue inflammation and apoptotic mediators are thought to be related to the pathophysiology of PGB-induced neurotoxicity (28). Administration of a high dose of PGB in animal models disrupts p38 mitogen-activated protein kinase (p38-MAPK) signaling (29). Disruption of p38-MAPK-mediated signaling promotes temporal lobe epilepsy and induces neuronal hyperexcitability (30-32). Dysregulation of the c-Jun N-terminal kinases (JNKs) pathways may also be responsible for PGB-induced neurotoxicity (29, 30, 32, 33).

Acute or chronic toxicity of PGB induces encephalopathy (24, 25) that can cause obvious seizures or epileptiform activity. There is evidence that PGB is associated with constant triphasic waves (TWs) and slow background activity w (34) which is characteristic of toxic metabolic encephalopathy (35).

In the current review, almost all of the authors of selected case reports did not report the seizures of their cases in detail. 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 (36). Although the EEG findings of epilepsy were reported in three cases who suffered from encephalopathy (24, 25). Myoclonus or negative myoclonus are known as reversible PGB side effects (36). According to evidence, induction of negative myoclonus by PGB may happen in patients who receive therapeutic doses or in patients with normal kidney function (36). 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 (37, 38). Due to its ‘‘seizure-like” nature, physicians might interpret this adverse drug reaction as a true seizure. However, it leads to unnecessary and aggressive management (39).

PGB can cause serotonin syndrome, especially when it is combined with other serotoninergic agents (40). Additionally, in the systematic review of PGB-associated movement disorders, myoclonus was observed in 12.7% (39/305 cases) of cases (41).

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 1 hour, which is sufficient to induce neurotoxicity (42). PGB is not metabolized and is eliminated by the kidney with an elimination half-life of 6 hours. The clearance of PGB is linearly correlated with creatinine clearance. Also, the reduction of the glomerular filtration rate (GFR) of PGB and its accumulation in serum plays an important role in its toxicity (43, 44). 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 (25, 40, 45) 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 men. Also, except for a lower volume of distribution in women in comparison to men, no gender variation in the pharmacokinetics of PGB has been observed (46). Although as a rule, the seizure threshold in females is lower than in men (14, 47). While estrogen is known to increase the risk of seizures, progesterone has an inhibitory effect. Furthermore, estrogen activity reduces gamma-aminobutyric acid (GABA-A) receptor inhibition, increases the excitation of glutamate receptors, and enhances excitatory neuronal synapses. Though, the majority of PGB-induced seizures were observed in cases that were over fifty years old and were at menopause stage that had low levels of estrogen. About two-thirds of females with PGB-induced seizures were older than 50 years old. However, renal function

in the elimination of PGB plays a more critical role in comparison to other factors like age or gender (3). According to Semel, Murphy et al. (2010), the relative risks for PGB-induced adverse drug reactions had a positive correlation with PGB dose, while no correlation was found with age (48).

5. 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 in therapeutic dose. The dosages taken by patients who used the drug for therapeutic purposes were much lower than in the other two groups. More detailed studies are needed to determine the risk factors for PGB-induced seizures.

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Table 1. PubMed 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])

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

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

the summarized data belongs to the case

Authors(year) (ref)	Cases	Seizure /sample size	Gender #	Median of Age (years) #	Dose of PGB	Risk factors	Others
Isoardi (2020)(20)	All cases	10/ 488	57% male	41	Median= 1200 mg		
	PGB only intoxicated	3/58	71% male	39	600mg 900mg 1800mg	pre-existing seizure disorder in one case (600mg)	All seizures were self-limiting and lasted approximately 1 minute.
	recreational PGB abusers	4/121	81% male	36	Median =900 mg		
Dufayet (2021)(49)	All cases (recreational PGB abuser and suicidal attempt)	2/382	5.3/1 male/female	15	NR	NR	Only adolescence was reported
Ryan(2016)(50)		1/56	54% male	44	Unknown	NR	The patient had a past history of seizure and presented 2 episodes of seizures
Tambon (2021)(51)	PGB in co-consumption	6/185	72.5% male	24		Co -consumption drugs	
	PGB alone recreational abuse	1/73	Female ##	15 ##	1200 mg ##	NR	

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

Authors(year) (ref)	**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 2 minutes and stope 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)(52)	single	54	female	3825	-	Intentional overdose	
Reedy(2010)(23)	single	16	male	2700 mg ingested and insufflated	-	Intentional over dose	GTC 1- hour latter
Reedy(2010)(23)	single	17	male	? ingested and insufflated	-	Intentional over dose	One self-limited and one treatment-limited episodes of GTC
Hsiao(2022)(24)	Multiple	51	Female	1200 and 1000	Multi-drug abuser and antiviral drug	Abuse drug	PRES
Ozturk(2019)(37)	single	23	Female	3000-4500 mg by nasal inhalation		Abuse drug	

Haji (2021) (53)	multiple	51	female	300 mg BID	Tapentadol	Therapeutic use	
Haji (2021) (53)	multiple	54	female	75 mg BID one year	Tapentadol, Aspirin, Propranolol, Duloxetine, Amitriptyline, Frusemide, Elitriptan.	Therapeutic use	

(GTC) = generalized tonic-clonic seizure, DM= diabetes mellitus, HTN= hypertension, CKD=chronic kidney disease, PRES= Posterior Reversible Encephalopathy Syndrome

Fig 1. Flow chart of the study selection process based on PRISMA