Gabapentin-Associated Movement Disorders

Subjects: Neurosciences

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Gabapentin (GBP) is U.S. FDA-approved for the adjunctive treatment of focal seizures and the treatment of postherpetic neuralgia. GBP also exhibits analgesic properties, often used as the first line in managing neuropathic pain. GBP-induced movement disorders are under-recognized adverse drug reactions. They are commonly not discussed with patients, and their sudden occurrence can lead to misdiagnosis of a “seizure-like” condition. Also, first-contact physicians might treat them as seizures or psychiatric comorbidities, leading to unnecessary tests and aggressive management.

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1. Myoclonus

Myoclonus was the most common movement disorder described with gabapentin (GBP), corresponding to 66.17% of the cases. The incidence of myoclonus varied from 1.09 to 21.05%, and the incidence was not affected by sex. The presentation of GBP-induced myoclonus was generalized myoclonus [1], multifocal [2], and focal [3]. A paradoxical aggravation of benign adult familial myoclonic epilepsy was reported in the literature [4]. Interestingly, some individuals presented with frequent unexplained falls, which can sometimes be misinterpreted in mental health settings, with hypotension or sedation caused by other medications [5]. Noteworthy, is that Hui et al. reported a case of jaw myoclonus leading to dysphagia with an inability to drink liquids [3]. Three patients from the Desai et al. case series that were treated with gabapentin had myoclonic jerks on the side contralateral to their epileptic focus. This finding may suggest that brain areas with antecedent dysfunction are more vulnerable to the toxic effects of calcium channel blockers [6].

Myoclonic symptoms can lead to significant distress or impaired function. One patient developed a myoclonus interfering with ambulation [5], and another had his speech impacted by the myoclonus of the lower facial muscles [3]. However, there were cases where myoclonic symptoms were tolerable and did not affect daily living activities, going clinically unnoticed without specific questioning [7].

Some, but not all, patients who experienced myoclonus presented with altered mental status. A toxic encephalopathy was observed in individuals who developed negative myoclonus secondary to gabapentin [8]. Chau et al. reported a patient with Creutzfeldt–Jakob disease-like syndrome induced by gabapentin toxicity, in which

electrodiagnostic studies showed periodic sharp wave complexes [9]. A similar clinical manifestation with electrodiagnostic studies was already observed with amitriptyline [10] and fluoroquinolones [11].

The neurophysiological source was cortical and subcortical. Interestingly, Scheyer et al. reported a reflexive response of myoclonus only with high doses of GBP [12]. Therefore, the source of myoclonus can be directly associated with the concentration of GBP. However, most articles did not report electrodiagnostic studies or a detailed clinical description of myoclonus for a clear diagnostic assumption of this hypothesis. Pierce et al. reported a 46-year-old female presenting with a triad of hearing loss, myoclonus, and confusion. GBP concentration was elevated, and hemodialysis was performed with complete recovery of the neurological symptoms [13]. This interesting case shows a possible association between cortical and subcortical myoclonic sources [14]. One probable cause of hearing loss in this individual could be the tensor tympani myoclonus [15].

Reeves et al. reported an association between myoclonus frequency and GBP dose [1]. Hence, researcehrs can hypothesize that the GBP-induced myoclonus is more likely to be a linear dose-dependent adverse effect rather than a threshold effect. It is worth mentioning that GBP exhibits nonlinear (zero-order) kinetics due to the saturable absorption [16]. Therefore, levels of GBP do not increase in proportion with increasing doses. In this context, Healy et al. reported a patient having myoclonus with GBP and pregabalin on different occasions [17].

One important fact to mention was the association between possible intoxication doses of GBP and kidney failure. Zhang et al. considered renal dysfunction a significant risk factor for developing myoclonus associated with GBP [18]. The case reported by Holtkamp et al. can support this hypothesis because myoclonus only occurred when the individual renal function became worse [19]. However, GBP-induced myoclonus was already observed in previously healthy individuals [20]. Noteworthy, GBP does not undergo hepatic metabolism and is primarily excreted unchanged in the urine. Therefore, renal excretion is the primary pathway for the systemic elimination of GBP, and subjects with poor renal clearance require dose adjustment to prevent elevated plasma concentrations and adverse side effects [21]. Refractory epilepsy [22], diffuse brain damage [8], higher doses of GBP [13], and renal function [23] were the most commonly reported risk factors for developing GBP-induced myoclonus. Individual differences in the occurrence of myoclonic jerks with GBP may be based on genetics or co-morbidities.

The mechanism of GBP-induced myoclonus is probably related to the serotoninergic hypothesis similar to that proposed for buspirone-associated movement disorders [24]. Klawans et al. induced myoclonus in young guinea pigs by administering the serotonin precursor, 5-hydroxytryptophan [25]. Serotonin blood levels are increased in healthy people exposed to GBP [26]. But, there is no evidence of GBP directly acting on serotonin receptors [27].

Huppertz et al. reported that, in GBP-induced myoclonus, the therapeutical dose of GBP should be maintained because the myoclonus will eventually improve with time [7]. But, some authors attempted to reintroduce GBP, and myoclonus reappeared [28]. Ahmad et al. stated that a slow de-escalation should be conducted to avoid developing chronic side effects [29]. Myoclonus secondary to GBP had the worst prognosis among the GBP-induced movement disorders, with only 79.24% of the individuals fully recovering.

2. Dyskinesia

The presentation of GBP-induced dyskinesia was ballism [30], chorea [31], hemichorea [32], choreoathetosis [33], and orofacial dyskinesia [34]. Shin et al. reported a 44-year-old male with chorea who had worsened choreiform movements after administering GBP for his restless legs syndrome [31]. Bonakis et al. described a similar case in which the individual was diagnosed with paroxysmal kinesigenic dyskinesia worsened by GBP [35].

The occurrence of dyskinesia associated with GBP widely varied in the literature. Choreoathetosis was observed in 7.1% of the GBP users when this side effect was a secondary outcome [36]. Some risk factors proposed for GBP-induced dyskinesia were cognitive impairment [37] and a history of previous movement disorder [38].

Aksoy et al. reported an interesting case of a 70-year-old male presenting with generalized choreiform movements with pramipexole, pregabalin, and gabapentin on different occasions [39]. This case can support a similar mechanistic hypothesis for these drugs leading to chorea, which can be associated with a dopaminergic pathway. Another possible mechanism is related to the GABAergic effect. In rat models, GBP decreased the activity of GABA neurons in the substantia nigra [40]. It is important to note that not all patients who take GBP experience chorea. This suggests that certain patients may have unique neurophysiological factors that make them more susceptible to this side effect.

The most common management was the discontinuation of the offending drug. Some authors reported administering other drugs to improve dyskinetic symptoms, such as diphenhydramine [41]. The full recovery rate of dyskinesia associated with GBP was 88.23%, above the mean data for GBP-induced movement disorders.

3. Dystonia

Dystonia was the third movement disorder most commonly reported with GBP. Interestingly, the population affected by GBP-induced dystonia had a lower mean age when compared to the other GBP-induced movement disorders. It is worth mentioning that this is a common finding among drug-induced movement disorders [42][43]. Most individuals presented with segmental dystonia [44], but status dystonicus [1], generalized dystonia [45], and axial dystonia [46] were also observed. Alford et al. described an individual who developed myotonia associated with dystonia [46].

Reeves et al. reported a case of a 23-year-old female with a history of epilepsy who was on carbamazepine and was prescribed GBP for panic attacks. The patient reported muscle twitches after using 1200 mg/day of GBP for four days. Her movements were of small amplitude and possibly dystonic or myoclonic. Reeves et al. described another patient with drug-resistant epilepsy who was on GBP 600 mg three times a day for one month and suddenly presented an oculogyric crisis, retrocollis, opisthotonic posturing, and repetitive jaw clenching. Electroencephalogram monitoring was normal. He was treated with 2 mg IV lorazepam, and his abnormal movements ceased after being present for approximately 15 h. After GBP discontinuation, the movements did not recur [1]. Both reports by Reeves et al. are important because the individuals had a delayed diagnosis due to being misdiagnosed as having a psychiatric disorder [47].

Apparently, the GBP dose is related to the occurrence of dystonia [44]. Also, some authors reported a synergistic effect with some medications, such as propranolol [45] and anesthetic agents [46]. Rohman et al. described a 26-year-old male who used a GBP single dose of 1600 mg for recreational abuse and developed cervical dystonia [48]. There has been a concerning increase in the abuse of GBP, and previously unknown adverse effects of this medication are being discovered. Recently, there have been reports of lethal overdoses caused by this once-believed harmless drug [49]. Therefore, the study by Rohman et al. provides a new possible clinical manifestation to be observed when there is suspicion of recreational abuse of GBP.

A proposed mechanism for GBP-induced dystonia is the abnormal concentrations of different monoamines. It was already observed that catecholamine depletion by alpha-methyl-para-tyrosine can cause acute dystonia in healthy volunteers [50]. Bernal et al. proposed that the dystonia observed with GBP was probably related to an increased GABAergic effect leading to decreased paroxysmal discharges, causing an increased dopaminergic effect [44]. Another possible explanation can be related to the increased serotonin levels observed with GBP [26]. An association between dystonia and the serotonergic system was already reported due to basal ganglia serotonin and serotonin–dopamine interactions [51].

The management was GBP discontinuation and lorazepam [1] or procyclidine intravenously [48] to shorten the recovery time. Palomeras et al. reported improved dystonic symptoms after reducing the adjunctive drug without changing the GBP dose [45]. A total of 83.33% of the patients with PGB-induced dystonia had a full recovery. One patient did not recover, and the persistence of his abnormal movements in the upper right limb throughout the follow-up was observed [44].

4. Akathisia

Childers et al. reported two cases of akathisia secondary to GBP therapy. Both patients used GBP 900 mg/day and fully recovered within two days of GBP discontinuation. The authors stated that brain-injured individuals are more sensitive to GBP therapy; consequently, this subgroup of GBP users more commonly develops side effects with even lower doses of GBP [52]. See et al. described a 76-year-old female with neuropathic pain managed with GBP 3600 mg/day. The patient developed akathisia due to GBP withdrawal, which is a unique report because this is the only report of a movement disorder, besides tremors and ataxia, associated with GBP withdrawal syndrome [53]. Possible explanations for GBP-induced akathisia could be related to the serotoninergic and dopaminergic hypothesis. Noteworthy, is that GBP does not affect 5HT2A commonly reported receptor associated with drug-induced akathisia [54]. Interestingly, GBP was already reported to improve akathisia symptoms caused by antipsychotics [55][56].

5. Stuttering

The occurrence of stuttering associated with GBP has been rarely reported. Interestingly, all the patients with stuttering following GBP therapy fully recovered after drug discontinuation. Nissani et al. probably reported the first

case of stuttering secondary to GBP. According to the authors, the patient was a middle-aged female with epilepsy, managed with phenytoin. She was then admitted for an “intractable seizure” when GBP was started, after which she developed stuttering. Four days after GBP discontinuation, the stuttering resolved [57]. In another case report, a 66-year-old man with postherpetic neuralgia was managed with GBP. After some days, the patient complained of stuttering, and GBP therapy was discontinued, with complete recovery of the symptoms [58]. Zeldin et al. reported a 62-year-old male with chronic back pain for whom methylprednisolone and GBP 300 mg thrice daily were started. After two days on this drug regimen, the patient presented stuttering, which started twenty minutes after taking GBP. Neuroimaging was unremarkable. GBP was gradually tapered, and the stuttering improved [59].

Stuttering is believed to occur due to hyperactivity in the brain’s right hemisphere, abnormal coordination between speech planning and execution centers, and abnormal dopamine concentrations [60]. Animal models showed that GBP causes abnormal dopamine concentrations in the striatum [61]. In this way, the abnormal levels of this neurotransmitter may lead to dysfunction between the motor cortex and Broca’s area. Pregabalin, another GABA analog, was already observed with stuttering [62]. Therefore, this side effect may be a class effect of GABA analogs. Interestingly, GBP was also effective in managing neurogenic stuttering [63]. Therefore, GBP may provoke or reduce stuttering, which the multiple interacting neurotransmitter systems can explain.

6. Myokymia and Parkinsonism

Only one study reported myokymia associated with GBP use, but the drug was probably at toxic levels. The patient was a 69-year-old man taking GBP in a prescribed dosage of 9600 mg/day. He had a previous history of peripheral neuropathy, traumatic brain injury, amnesia, and post-traumatic stress disorder. He presented with muscle spasms and falls. He had focal and segmental myokymia observed in his lower extremities, which were worse in the calves than in the thighs. The GBP level was 25.8 µg/dL (therapeutic range, 2–20 mcg/mL). After reducing the daily dosage of GBP, the patient presented improvement in his abnormal movements [64]. Elevated serotonin levels may partially explain GBP-induced myokymia. Noteworthy, is that flunarizine, a calcium channel inhibitor, shares a similar mechanism of action with GBP. And, this drug was already reported to cause myokymia [65]. Although GBP-induced myokymia is scarce, there are many reports about myokymia managed with GBP. Superior oblique myokymia was already observed to improve with GBP therapy [66]. GBP is believed to alleviate myokymia by causing a membrane-stabilizing effect that avoids peripheral nerve excitability [67].

Gabapentinoids affect several neurotransmitters, including dopamine and serotonin. It is believed that their chronic effect may increase the risk of parkinsonism. Pacheco-Paez et al. assessed 5,653,547 reports, of which 4881 individuals with Parkinson’s disease had a chronic use of GBP. The authors reported an increased odds ratio (OR = 2.16, 95% CI 2.10–2.23) of Parkinson’s disease in GBP users [68]. Ri et al. performed a case-crossover study in the Japanese population to assess the risk of parkinsonism with gabapentinoids. They observed that exposure to gabapentinoids (adjusted OR, 2.12; 95% CI, 1.73–2.61) was associated with an increased risk of developing parkinsonism [69].

7. Gabapentin and Pregabalin-Associated Movement Disorders

Pharmacologically, GBP and pregabalin bind to the alpha-2-delta protein, a subunit of the voltage-gated calcium channels and a receptor involved in regulating neuronal excitability. The inhibition of alpha-2-delta receptors decreases calcium influx at the nerve terminal, reducing the release of excitatory neurotransmitters (glutamate, noradrenaline), thereby reducing pain signaling. Here, researchers would like to compare the epidemiological profile of the individuals affected by GBP and pregabalin-associated movement disorders (**Table 1**) [62].

Table 1. Gabapentin and pregabalin-associated movement disorder.

MD		Gabapentin General Data	Pregabalin General Data [a]
Cases (%)		204 (100%)	305 (100%)
Movement disorders	Akathisia	3 (1.47%)	1 (0.32%)
	Ataxia	NA	184 (60.32%)
	Dyskinesia	22 (10.78%)	1 (0.32%)
	Dystonia	7 (3.43%)	1 (0.32%)
	Myoclonus	135 (66.17%)	39 (12.78%)
	Myokymia	1 (0.49%)	0 (0%)
	Parkinsonism	1 (0.49%)	8 (2.62%)
	Restless legs syndrome	0 (0%)	1 (0.32%)
	Stuttering	3 (1.47%)	0 (0%)
	Tremors	NA	61 (20%)
	Others	32 (15.68%)	9 (2.95%)
Continent (%)	Africa	0 (0%)	0 (0%)
	Australia	1 (0.49%)	0 (0%)
	Asia	30 (14.70%)	40 (13.11%)
	Europe	81 (39.13%)	68 (22.29%)
	N. America	91 (44.60%)	196 (64.26%)
	S. America	1 (0.49%)	1 (0.32%)

MD		Gabapentin General Data	Pregabalin General Data [a]
Sex (%)	Female	52 (25.49%)	21 (6.88%)
	Male	60 (29.41%)	25 (8.19%)
	Unknown	92 (45.09%)	259 (84.91%)
Age (year)	Rg	10–89 (Md: 57)	23–94 (Md: 66.5)
	Mn	54.54 (SD: 17.79)	62.89 (SD: 18.12)
Dose (Mn mg)		1324.66 (SD: 1117.66; Rg: 100–9600; Md: 1033)	238 (SD: 136.95; Rg: 50–600; Md: 150)
MD onset	Range	1 h–4 years	1 day–9 months
	Mean	4.58 weeks (Sd: 8.08; Md: 1)	9.48 days (Sd: 16.78; Md: 3)
MD recovery	Range	1 day–12 months	1 day–6 months
	Mean	4.17 days (Sd: 4.87; Md: 2.5)	12.17 days (Sd: 22.13; Md: 2.5)
Follow-up—% CR (number of reports)		82.5% (66/80)	100% (18/18)

Abbreviations: CR: complete recovery; MD: movement disorder; Md: median; Mn: mean; NA: not available/not applicable; Rg: range (minimum–maximum); SD: standard deviation. In the "Others" subgroup are cases not specified about the movement disorder, such as extrapyramidal symptoms. [a] Data extracted from the reference Rissardo et al. (2020) [62].

to mention regarding myoclonus and these gabapentinoids drugs is the fact that gabapentin has risk factors that are usually observed in the population affected, such as refractory epilepsy, diffuse brain damage, and renal function. But, pregabalin-induced myoclonus does not have significant risk factors.

Interestingly, GBP is more commonly reported with dystonia and dyskinesia. On the other hand, pregabalin was more frequently described with parkinsonism. Recent studies assess the risk of gabapentinoids as a class in developing Parkinson's disease. Therefore, based on this present data, future studies should assess the effect of GBP and pregabalin with sensitive analysis because pregabalin may be a major risk factor than GBP for the development of Parkinson's disease.

The individuals that developed a movement disorder secondary to GBP had the worst prognosis than those who had one secondary to pregabalin. Noteworthy, is that the description of the follow-up of pregabalin-induced movement disorder was only provided by 18 articles. Therefore, further assumptions regarding the follow-up of pregabalin-associated movement disorder cannot be provided.

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