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CASE REPORT



Pregabalin withdrawal in patients without psychiatric disorders taking a regular dose of pregabalin: A case series and literature review

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Abstract

Pregabalin is a drug that can cause psychiatric symptoms via pregabalin withdrawal. Prior reports on pregabalin withdrawal have mainly focused on cases with pregabalin dependence or abuse, and little attention has been paid to patients who are prescribed regular doses of pregabalin. Herein, we report three cases of pregabalin withdrawal in patients without psychiatric disorders, taking regular doses of pregabalin, who developed psychiatric symptoms such as insomnia and anxiety after abrupt discontinuation of pregabalin. In addition, we conducted a systematic review of six case reports (previous studies) of pregabalin withdrawal under regular doses of pregabalin. Among the six cases, three patients had no comorbid mental or substance use disorders, the dose of pregabalin ranged from 150 to 600 mg/d, and the duration of pregabalin use ranged from a few weeks to many years. Of these six cases of pregabalin withdrawal, five had psychopathological symptoms, three had vegetative symptoms, and three had neurologic and physical complications. We concluded that since pregabalin withdrawal can occur even with regular doses and short-term use, clinicians must carefully reduce pregabalin doses when reducing or discontinuing treatment, paying close attention to withdrawal symptoms. Our case series sheds light on the scant evidence from previous research on physical dependence in patients who are taking regular doses of pregabalin. Furthermore, our cases were also valuable in demonstrating that pregabalin withdrawal can occur even after a relatively short period of 2 months.

KEYWORDS

anxiety, dependence, insomnia, pregabalin, withdrawal

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1 | INTRODUCTION

Pregabalin is a drug prescribed for neuropathic pain, anxiety disorders, and partial epilepsy.¹⁻³ In Japan, pregabalin is approved for neuropathic pain (150-600 mg/d) and pain associated with fibromyalgia (150-450 mg/d). Pregabalin is presumed to exert its effect by binding to the $\alpha 2\delta$ subunit of voltage-gated Ca^{2+} channels, thereby inhibiting Ca^{2+} influx into the nerves and decreasing neurotransmitter release.⁴

Pregabalin can cause psychiatric symptoms during withdrawal. Prior reports on pregabalin withdrawal have mainly focused on cases with pregabalin dependence or abuse; previous studies have not focused on patients who were prescribed regular doses of pregabalin.^{5,6} Herein, we report three cases of pregabalin withdrawal in patients without psychiatric disorders taking regular doses of pregabalin, who developed psychiatric symptoms such as insomnia and anxiety after the dose of pregabalin was reduced. Written informed consent was obtained from each patient for the publication of this case series. Furthermore, we conducted a systematic review of previous case reports that reported pregabalin withdrawal under regular doses of pregabalin.

2 | CASE PRESENTATIONS

2.1 | Case 1

A 39-year-old man visited the psychiatric department of our hospital. The patient's medical history included cervical spondylosis and right upper extremity neuropathic pain. The patient had no history of mental disorders. Two months before the visit, the patient was started on pregabalin for right upper extremity neuropathic pain and was administered 600 mg/d of pregabalin and 200 mg/d of celecoxib at the time of the visit. The patient experienced symptoms of cold 9 days before the visit; therefore, all prescription drugs were discontinued at his discretion. Seven days before the visit, the patient experienced dyspnea, loss of appetite, insomnia, and anxiety. With these symptoms as the chief complaint, the patient visited our emergency department for 3 consecutive days (4-6 days before the visit). The patient's blood test results were normal; however, due to prolonged respiratory and psychological symptoms, 4 days before the visit, the patient was admitted to the otolaryngology department of the hospital. The patient's appetite and cold symptoms improved during hospitalization, and he was discharged on the fifth day of hospitalization. However, the patient was referred to a psychiatrist on the day of discharge due to worsening of insomnia and anxiety.

The patient had severe insomnia. Palpitations, restlessness, and anxiety were the main complaints. No psychotic symptoms, such as hallucinatory delusions or mood episodes, were observed. As the patient was unaware that the discontinuation of pregabalin could potentially have caused these symptoms, he did not mention pregabalin discontinuation. As an initial treatment, zolpidem 10 mg/d was prescribed for insomnia.

Two days later, his insomnia and psychiatric symptoms persisted. A detailed review of the patient's medical history during this visit suggested the possibility of pregabalin withdrawal; therefore, 300 mg/d of pregabalin was resumed from the same day. His respiratory distress, palpitations, and insomnia rapidly improved within the next few days. The dose of pregabalin was returned to 600 mg/d. After 16 days, the patient's anxiety symptoms disappeared, no sleeping pills were required, and the follow-up was completed.

2.2 | Case 2

A 74-year-old woman was referred to the psychiatry department of our hospital. She had a history of shingles. She had no history of mental disorders. She was being treated with 150 mg/d of pregabalin for postherpetic neuralgia for 10 years and brotizolam of 0.25 mg/d for insomnia for 11 years. A year before the referral, the patient was instructed by her orthopedic surgeon to reduce the intake of pregabalin. However, she consistently failed to reduce the dose of the medication owing to physical and psychological discomfort. Sixteen days before her referral, pregabalin was switched to tramadol hydrochloride acetaminophen combination tablets due to pain. Nine days before the referral, the patient experienced cold sweats, headaches, and finger tremors. In addition, 6 days before the referral, the patient started to experience insomnia, loss of appetite, dyspnea, lacrimation, epigastric discomfort, insomnia, and depression. Two days before the referral, the patient felt restless and suicidal, and she attempted suicide by strangling herself with a towel, after which the patient was brought to our emergency department by her family. Examinations conducted in the emergency room, including head computed tomography (CT) scans, were normal. Subsequently, she was referred to the psychiatric department for continued suicidal ideation and restlessness (16 days after pregabalin discontinuation).

The patient awoke several times every 1-2 hours and consumed very little food. The patient experienced depression, restlessness, anxiety, and suicidal ideation. No manic or psychotic episodes were observed. Following this, pregabalin withdrawal was suspected, and pregabalin 150 mg/d was resumed.

Two days later, her psychiatric symptoms, except for insomnia, had disappeared. Her insomnia had also improved rapidly after resuming pregabalin. Therefore, patient follow-up was terminated.

2.3 | Case 3

A 69-year-old man was referred to the psychiatry department of our hospital. The patient's medical history included hypertension and sciatica, with no history of mental illness. The patient was being treated with 40 mg/d of telmisartan for hypertension. The patient was administered 600 mg/d of pregabalin for sciatica for 19 years. The patient had been instructed by his doctor to reduce pregabalin intake according to his pain. However, the patient found this challenging since he previously experienced chest tightness during the dose reduction

TABLE 1 Summary of pregabalin withdrawal in cases taking a regular dose of pregabalin

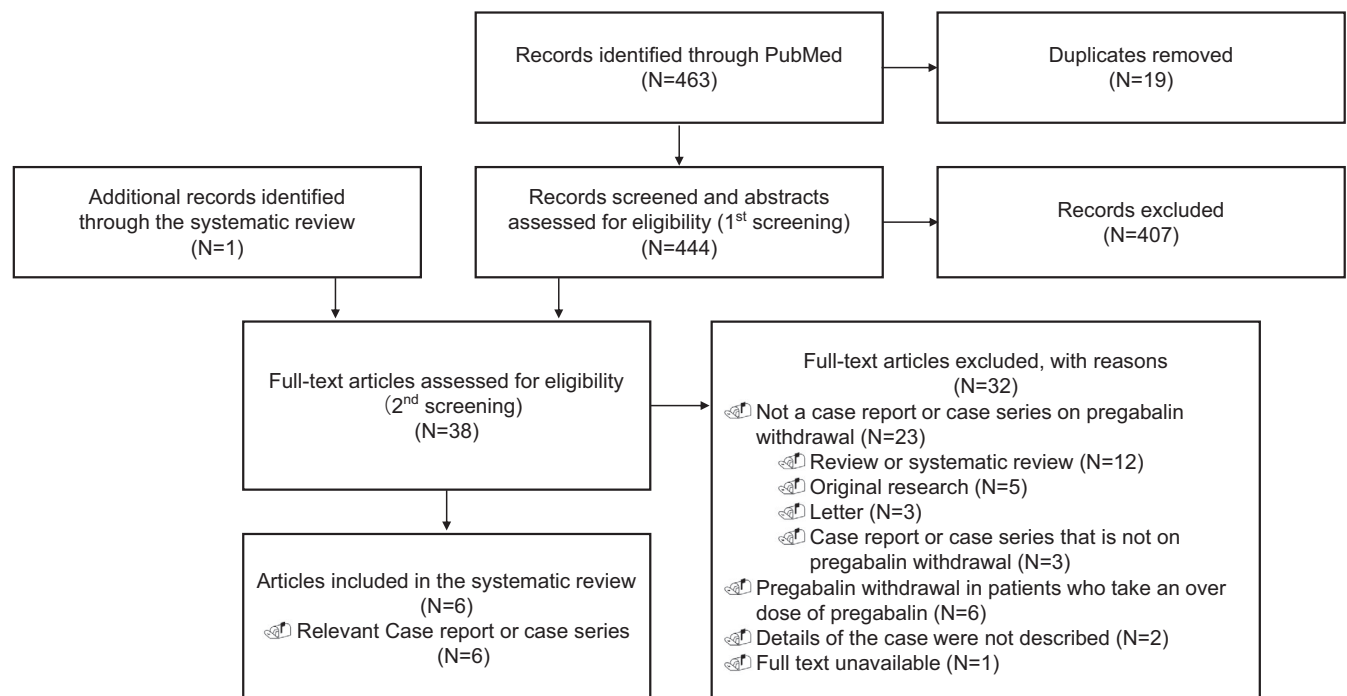
Case report citation	Case	Psychiatric disorders	PGB maximum dosage	PGB duration	Discontinuation or taper period
Uçar 2020 ⁸	30 F	None	150 mg/d	45 days	Discontinuation
Naveed 2018 ⁹	62 F	GAD and DD	450 mg/d	ND	ND
Du 2017 ¹⁰	52 F	None	150 mg/d	Many years	Discontinuation
Driot 2016 ¹¹	24 F	GAD, DD, PD, and anorexia	300 mg/d	A few weeks	No tapering or discontinuation
Gahr 2013 ¹²	38 F	PD and DD	600 mg/d	2 months	25 mg/d
Oaklander 2005 ¹³	80 F	None	375 mg/d	49 weeks	0
Case 1	39 M	None	600 mg/d	2 months	0
Case 2	74 F	None	150 mg/d	10 years	0
Case 3	69 M	None	600 mg/d	19 years	0

Abbreviations: DD, depressive disorder; GAD, generalized anxiety disorder; ND, not described; PD, personality disorder; PGB, pregabalin.

period. The patient suddenly stopped pregabalin intake 2 days before the referral as he had lost the prescribed pregabalin. The patient started to experience chest tightness, suffocation, chills, and insomnia from the same evening. He visited our emergency department for 2 consecutive days after pregabalin discontinuation, complaining of

the above symptoms. Blood tests and chest CT scans were normal. An emergency physician considered that the patient had psychiatric issues and immediately referred him to the psychiatric department.

The patient started to experience insomnia and was experiencing depression, chest anguish, chills, and loss of appetite,

**FIGURE 1** Flowchart of the study selection process for the studies included in the review

Onset of symptoms after discontinuation of PGB	Withdrawal symptoms		
	Psychopathologic symptoms	Vegetative symptoms	Neurologic and physical complications
48 hours	Insomnia, dysphoria, delusions, visual hallucinations, and the idea of harm	ND	ND
ND	Anxiety, fear, insomnia, suicidal ideations, and feeling of going crazy.	Tremors, dyspnea, palpitations, and dizziness.	Chest pain, extreme weakness of legs, and aches.
4 days	ND	ND	Tonic-clonic seizure
ND	Asthenia, insomnia, and suicidal ideas	Tremors, sweating	ND
10 days	Psychomotor agitation and craving	Hypertension, tachycardia, and tremor	ND
30 hours	Visual and auditory hallucinations, alexia, distorted color perception, delirium, terror	ND	Nausea, headache, "imbalance,"
2 days	Insomnia, anxiety, and restlessness	Palpitations	difficulty in breathing, and loss of appetite
7 days	Insomnia, depressed mood, anxiety, restlessness, suicidal ideation, and psychological discomfort	Tremor, cold sweats, lacrimation	Physical discomfort, headache, appetite loss, dyspnea, and epigastric discomfort
1 day	Insomnia and depressed mood	None	Chest tightness, suffocation, chills, and loss of appetite

with no psychotic episodes or symptoms. Pregabalin withdrawal was then suspected, and pregabalin was immediately resumed at 600 mg/day.

After resuming pregabalin, symptoms such as chest anguish, chills, insomnia, loss of appetite, and depressed mood improved promptly. After 7 days, all symptoms that appeared after discontinuation of pregabalin were improved; therefore, psychiatric follow-up was terminated. He was subsequently prescribed to continue 600 mg/day of pregabalin, and no recurrence was observed.

3 | LITERATURE REVIEW

This qualitative systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations for reporting systematic reviews and meta-analyses.⁷

3.1 | Literature search

A PubMed search was conducted (last search: April 4, 2021) with combinations of the following keywords: "pregabalin"[Title/Abstract] AND ("Abuse"[Title/Abstract] OR "withdraw"[Title/Abstract] OR "Discontinuation"[Title/Abstract])" Studies in any language that met the following criteria were included; (a) patients taking a regular dose of pregabalin up to 600 mg/d; (b) patients experiencing pregabalin withdrawal (psycho pathogenic symptoms,

vegetative symptoms, or neurologic and physical complications) after discontinuation or taper of a regular dose of pregabalin; (c) studies detailing the following information on cases of pregabalin withdrawal: age, sex, pregabalin doses, withdrawal symptoms, and the course of pregabalin withdrawal; 4) case report or case series in full text.

3.2 | Process of study selection

The screening of eligible publications was carried out independently by Ha.I and MT First, the titles and abstracts of all publications were reviewed. In the first screening, we included studies with designs other than case reports or case series to detect studies that may have been missed in our systematic literature search. Next, the full text of potentially relevant publications was reviewed, and ineligible publications were excluded. Discrepancies were resolved by consensus, and any disagreement was resolved by a systematic and thorough discussion with Hi.I.

3.3 | Data extraction and risk of bias assessment

The following data were extracted by Ha.I and cross-checked by M.T: (a) author, year of publication; (b) patients' key characteristics, such as age, sex, and comorbid psychiatric disorders; (c) Pregabalin dosage and duration; (d) withdrawal symptoms of pregabalin (psycho pathogenic symptoms, vegetative symptoms, and neurologic and



physical complications); (6) discontinuation or taper period of pregabalin, the onset of symptoms after discontinuation of pregabalin.

We decided not to conduct a risk of bias assessment because important information about pregabalin withdrawal was included in the inclusion criteria.

3.4 | Results of the literature review

Figure 1 shows a flow diagram of the literature search process. We identified 463 articles through the systematic literature search. Of these, six case reports (six cases) were identified in which withdrawal symptoms occurred in patients administered pregabalin at the usual dose of 600 mg/d or lower.⁸⁻¹³ Table 1 shows the demographic data and clinical symptoms of the six cases. Among these cases, three patients had no comorbid mental or substance use disorders. Among all patients, the dose of pregabalin ranged from 150 to 600 mg/d, and the duration of pregabalin use ranged from a few weeks to many years. Of these, five had psychopathological symptoms, three had vegetative symptoms, and three had neurologic and physical complications.

4 | DISCUSSION

In this case series, we present three cases of pregabalin withdrawal experienced after discontinuation in patients without a history of psychiatric or substance use disorders taking regular doses of pregabalin. Our case series sheds light on the scant evidence from previous research on physical dependence in patients taking regular doses of pregabalin. Furthermore, our cases were also valuable in demonstrating that pregabalin withdrawal can occur even after a relatively short period of 2 months.

On pregabalin withdrawal, our cases experienced psychopathological symptoms such as anxiety, restlessness, and insomnia; vegetative symptoms such as palpitations, sweating, and shedding tears were also observed, along with neurologic and physical complications, such as headache, dyspnea, and loss of appetite. The symptoms experienced by our patients after discontinuation of the regular dose of pregabalin were similar to those reported in previous studies of pregabalin and gabapentin, which has the same pharmacological mechanism as pregabalin.^{9,12-18} Considering that our patients had no psychiatric disorders, our diagnosis was reasonable because the symptoms were caused by pregabalin withdrawal. The package insert contains a warning that the abrupt discontinuation of pregabalin can induce symptoms such as insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea;¹⁹ however, it should be noted that other symptoms such as tremors, suicidal ideation, and hallucinations can also occur as withdrawal symptoms of pregabalin.

Possible mechanisms by which withdrawal from pregabalin may result in psychiatric symptom is unclear. However, considering that pregabalin and gabapentin have a common pharmacological

mechanism of binding to the $\alpha\delta$ subunit of voltage-gated Ca^{2+} channels and consequently reducing the release of excitatory neurotransmitters by inhibiting Ca^{2+} influx into the nerve⁴ and that the withdrawal symptoms of pregabalin and gabapentin are similar,^{9,12-18} this pharmacological feature may directly or indirectly cause withdrawal symptoms.

It is also interesting to note that our cases developed pregabalin withdrawal after discontinuing a regular dose of pregabalin. The intake of pregabalin in two patients was 600 mg/d, while that in one patient was 150 mg/d. As shown in Table 1, there have been only six prior cases of pregabalin withdrawal due to the discontinuation of regular doses of pregabalin. This study suggests that withdrawal can occur even in cases without pregabalin dependence or abuse. The dose and duration of pregabalin use were previously found to correlate with pregabalin withdrawal significantly.²⁰ Therefore, clinicians must be aware of the possibility of physical dependence with the long-term use of pregabalin, even at regular doses. It is also important to consider the duration of pregabalin use. Case 1 showed pregabalin withdrawal after only 2 months of pregabalin use, and previous reports have also shown pregabalin withdrawal in cases after a few weeks or 45 days of short-term pregabalin use.^{8,11} Case 1 was particularly worth reporting because it suggested that even a short period of a regular dose of pregabalin can cause physical dependence. Since the risk factors for physical dependence during the intake of a regular dose of pregabalin have not been fully elucidated, it may be necessary to gradually taper off the dose of pregabalin while paying close attention to pregabalin withdrawal symptoms, even if a regular dose is used for a short period of time. Further well-designed prospective studies are warranted to examine the incidence and risk factors of pregabalin withdrawal in patients taking regular doses of pregabalin.

5 | CONCLUSION

Since pregabalin withdrawal can occur even with regular doses and short-term use, clinicians must carefully reduce the dose of pregabalin when reducing or discontinuing treatment, paying close attention to withdrawal symptoms.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the paper. M.T and Ha.I conducted a systematic literature search. All authors agree to be accountable for all aspects of this study.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

Since this study was a case series and systematic review, it was exempted from the approval of the Ethics Committee. The Ethics Committee Akita University Graduate School of Medicine and Faculty of Medicine determined that there was no need to review this case.

INFORMED CONSENT

Written informed consent was obtained from each patient for the publication of this case series.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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