

Delirium After Pregabalin Withdrawal

ABSTRACT

Pregabalin is a γ -amino butyric acid analogue drug that is used in fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, spinal cord injury, and postherpetic neuralgia. Symptoms reported in association with pregabalin withdrawal include insomnia, gastrointestinal distress, tachycardia, and headache. This case report describes a 68-year-old patient who developed delirium after experiencing pregabalin withdrawal. Clinicians should be aware of the possibility of pregabalin withdrawal delirium.

Keywords: Pregabalin, delirium, drug withdrawal symptoms

Introduction

Pregabalin is a structural analogue of γ -amino-butyric acid (GABA), acting on the $\alpha_2\delta$ sub-unit of the P/Q type voltage-gated calcium channels in presynaptic neurons. It reduces the release of excitatory neurotransmitters in the central nervous system.¹ It has anticonvulsant, analgesic, and anxiolytic properties.² Pregabalin is approved for the treatment of fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, spinal cord injury, and postherpetic neuralgia by the US Food and Drug Administration.³ However, pregabalin is widely used off-label for a variety of conditions, including generalized anxiety disorder, social anxiety disorder, bipolar disorder, insomnia, and chronic pain conditions.⁴

Fibromyalgia is a chronic, debilitating condition associated with widespread chronic pain, chronic fatigue, sleep disturbances, somatic and cognitive symptoms, and often coexisting psychiatric symptoms for at least 3 months.

In patients with fibromyalgia, the recommended therapeutic dosage of pregabalin is 300 mg to 450 mg/d.³ The most common side effects of pregabalin are facial rash, dizziness, drowsiness, peripheral edema, and weight gain.¹ The discontinuation symptoms of pregabalin are agitation, anxiety, gastrointestinal distress, tachycardia, and palpitations.⁵ Delirium, psychosis, and visual hallucinations have been reported as potential adverse effects of the use of gabapentinoids.^{6,7} Nonetheless, few case studies chronicle these symptoms associated with pregabalin.⁸ This article details the case of an older woman who developed delirium after experiencing pregabalin withdrawal.

Case Presentation

A 68-year-old female with no significant personal or family history of psychiatric illness was brought to the emergency room with psychotic symptoms. The symptoms included a fluctuating course of drowsiness; confusion; disorientation as to time, person, and place; alternating consciousness; and severe visual hallucinations. Notably, 3 days before being seen in the emergency room, the patient abruptly decided to terminate her pregabalin therapy without seeking medical consultation. She had been prescribed 75 mg of pregabalin for fibromyalgia a year before, and the dosage gradually increased to 300 mg. The patient's family reports that after discontinuing pregabalin, she exhibited erratic behavior, increased confusion, disrupted sleep-wake cycle, and decreased appetite. The patient was anxious and had pressured speech.



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The patient was uncooperative during her clinical examination. She exhibited disorientation to time, person, and place and impaired attention and concentration. Results of evaluations, including complete blood count, liver function tests, serum electrolytes, blood sugar, thyroid function tests, kidney function tests, urine analysis, and electrocardiography were within normal limits. She had no fever. A computerized tomography scan of the brain and electroencephalography revealed no remarkable findings. Delirium was diagnosed following the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Of note, 1 mg/d of haloperidol was started in 2 divided doses. The patient's delirium improved considerably within 24 hours. Her symptoms improved and the delirium resolved within 48 hours, but she could not remember what had happened in the previous 3 days. The patient was discharged 3 days after appearing in the emergency room. Written consent was obtained from the patient.

Discussion

The case report describes a 68-year-old patient with fibromyalgia who developed delirium following pregabalin withdrawal. A total of 3 days before presentation, the patient discontinued her 1-year course of 300 mg/d of pregabalin. To the best of our knowledge, there are few similar reported cases. Fabio et al⁹ described a 76-year-old female patient with diabetes mellitus who became delirious after gabapentin withdrawal. Oaklander et al¹⁰ described an 80-year-old female patient with hypertension, hypothyroidism, hypercholesterolemia, macular degeneration, and glaucoma, who became delirious after pregabalin discontinuation. Gundogmus et al¹¹ described a 20-year-old female patient with no history of psychiatric illness, who became psychotic after pregabalin withdrawal. The patient received a high dosage of pregabalin (2700 mg/d) and, after discontinuation, displayed withdrawal symptoms, including paranoid ideas, auditory hallucinations, and mutism.⁹

Pregabalin is a novel medication that modulates GABAergic neurotransmission. It decreases the concentration of various neurotransmitters, including noradrenaline, serotonin, dopamine, glutamate, and substance P.¹ In addition, it binds to the $\alpha\delta$ subunit of voltage-gated calcium channels in various regions of the central nervous system. The abrupt discontinuation of pregabalin could have caused a rapid upregulation of the frontolimbic circuit mediated by calcium channels. There is a hypothesis that the mechanism for symptoms of gabapentinoid disruption is similar to that of ethanol and benzodiazepine, in which cessation increases the production of the enzyme responsible for producing GABA.¹² If GABA hypofunction is present in the central nervous system (including the hippocampus, prefrontal cortex, and the limbic cortical and subcortical regions), cognitive impairments can occur. Gabapentinoid taper is associated with an increased risk of delirium and confusion.^{8,12} This may potentially lead to delirium and may explain the

pathophysiology that occurs in this case. However, the discontinuation of pregabalin is considered clinically safe if reduced gradually over 1 week.⁹

In conclusion, physicians should be aware of the potential for pregabalin withdrawal delirium in elderly individuals and consider haloperidol as a possible effective treatment for delirium associated with pregabalin withdrawal. Further clinical experience and controlled trials are needed to evaluate delirium associated with pregabalin withdrawal.

Informed Consent: Informed consent was obtained from the patient.

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MAIN POINTS

- Physicians should be aware of the potential for pregabalin withdrawal delirium.
- Haloperidol as a possible effective treatment for delirium associated with pregabalin withdrawal.
- Tapered discontinuation of the pregabalin is considered clinically safe.