

Generalized Tonic-Clonic Seizure Related to Fluvoxamine Overdose: A Case Report

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Innov Clin Neurosci. 2026;23(7–9):43–45.

ABSTRACT: Selective serotonin reuptake inhibitors (SSRIs) have become a preferred treatment option for psychiatric disorders due to their relatively safe adverse effect profiles. Despite their widespread prescription and general safety, there is a need to better understand the adverse effects and potential complications of SSRIs, particularly in overdose situations. Fluvoxamine, an SSRI approved for treating obsessive-compulsive disorder (OCD), is typically safe within therapeutic doses but can lead to severe adverse drug reaction in cases of overdose. This report presents an infrequent occurrence of a generalized tonic-clonic seizure following an overdose of fluvoxamine in a 20-year-old nonepileptic female patient with OCD. The patient did not consume alcohol or any other medications that could have contributed to the seizure activity. She had no previous history of epilepsy or any known risk factors for seizures. The seizure occurred shortly after 1,500 mg of fluvoxamine ingestion. Even though it is generally considered safe at therapeutic doses, this case highlights the potential proconvulsant effect of fluvoxamine in overdose and underscores the need for clinician vigilance, particularly at high doses, and to consider the risks when prescribing pharmacotherapy. Further research is necessary to clarify the dose-related proconvulsant properties of fluvoxamine and to develop strategies for overdose scenarios. **KEYWORDS:** Fluvoxamine, overdose, seizure, SSRIs

The use of medications traditionally classified as antidepressants, which have become increasingly common in the treatment of various diagnoses beyond depressive disorders, has been growing over time.¹ Selective serotonin reuptake inhibitors (SSRIs), in particular, have emerged as a relatively safer choice with similar efficacy to drugs with broader adverse effect profiles, such as the class's predecessors, tricyclic antidepressants and monoamine oxidase inhibitors.¹ Although SSRIs are frequently prescribed and generally considered safe in most clinical scenarios, there remains a need to understand their yet-to-be-elucidated adverse effect potentials, identify unpredictable related conditions in overdose scenarios, and develop coping strategies accordingly.

Fluvoxamine, is an approved SSRI for the treatment of obsessive-compulsive disorder (OCD).² It is accepted for use in divided doses 3 times per day, with a maximum dose of 300 mg/day.² Although known for its safer therapeutic range and relatively milder side effect profile compared to tricyclic antidepressants, more data is needed in case of exposure to overdose in clinical scenarios. While it is not primarily identified with proconvulsant properties, cases of fluvoxamine overdose leading to seizure have been reported.^{2–6} Many of these reported cases also involve concomitant alcohol use or another high-dose medication intake during suicide attempts.⁵ Fluvoxamine overdose usually remains asymptomatic at doses of 1,000 mg, but mild clinical symptoms have been reported in the literature with up to 9,000-mg doses.⁶ Additionally, doses exceeding 1,000 mg can cause benign symptoms such as nausea, vomiting, abdominal pain, dizziness, tremors, and bradycardia.⁵ Serious adverse events such as altered consciousness, myoclonus, seizure, and coma have been reported at doses over 1,500 mg.^{2,5,6} Seizure cases associated with the therapeutic dosage of fluvoxamine are limited, and most cases have a history of prior seizures.³ This study aims to contribute to existing literature by discussing a

generalized tonic-clonic seizure case following high-dose fluvoxamine use. Our case is rare in the literature due to the absence of concomitant alcohol use and another high-dose medication intake along with fluvoxamine.

CASE REPORT

A 20-year-old female patient with a history of OCD, treated with 300 mg/day of fluvoxamine, was brought to the emergency department by her relatives after deliberately ingesting a high dose of fluvoxamine. The ingestion occurred at home approximately 2 hours before emergency department admission. Her initial complaints were nausea and dizziness, which began approximately 1 hour after consuming a single 1,500-mg dose of fluvoxamine. In addition to fluvoxamine, she was taking 15 mg/day of mirtazapine for sleep and appetite problems and did not report any additional overdose. She denied alcohol and substance use.

The patient was alert, oriented, and fully cooperative, with a Glasgow Coma Scale score of 15. Her vital signs were recorded as blood pressure of 110/75 mmHg, heart rate of 77 beats per minute, respiratory rate of 14 per minute, temperature 37° Celsius, saturation 99% within normal range, and they remained stable during 24 hours of monitoring. She was able to maintain her airway spontaneously. Neurological examination revealed no abnormalities. Following the recommendations of the National Poison Advisory Center, the initial plan included gastric lavage and administration of activated charcoal applied before psychiatric evaluation. Laboratory tests, including complete blood count, serum glucose, electrolytes, liver and kidney functions, and lactate and blood gas analysis, were requested, and all parameters were within normal ranges.

The patient was referred to psychiatry to evaluate the severity of her OCD symptoms and to assess current and prospective suicide risk. During a brief psychiatric interview in the emergency department, the patient

FUNDING: No funding was provided for this article.

DISCLOSURES: The authors have no relevant conflicts of interest.

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experienced a generalized tonic-clonic seizure, which was witnessed by the medical team. There were no preceding aura or warning signs reported by the patient. The event began with an abrupt loss of consciousness, accompanied by generalized muscle rigidity and upward gaze, consistent with the tonic phase, followed by rhythmic bilateral clonic jerking. The patient experienced urinary incontinence but no tongue-biting. The medical team immediately secured the airway and administered 10 mg of intravenous (IV) diazepam to terminate the seizure. Capillary blood glucose levels were within normal limits during the episode. Vital signs remained stable throughout, and no advanced airway intervention was required. The seizure lasted approximately 2 minutes without complication, and the patient was subsequently placed under monitored observation. A postictal phase of lethargy and confusion persisted for 20 minutes, during which no focal neurological deficits were observed.

This was the patient's first documented seizure episode, occurring 3 hours after ingestion. Notably, there were no clinical signs suggestive of status epilepticus. After evaluation by the neurology team, contrast-enhanced brain tomography and diffusion magnetic resonance imaging were performed to rule out possible etiologies, both of which yielded normal results. The patient received a loading dose of 1,500 mg IV levetiracetam, followed by maintenance treatment with 1,000 mg/day levetiracetam and an infusion of normal saline at 100 cc/hour. Her previous psychotropic treatment was temporarily discontinued. During the 24-hour observation period, no further seizure occurred. An electroencephalogram was not planned in the emergency setting. The patient was referred back to psychiatry for further evaluation.

During a detailed psychiatric interview, it was learned that the patient had been diagnosed with OCD for 5 years. She suffered from impaired functionality due to contamination obsessions, cleaning rituals, and prolonged periods in the bathroom. Her school performance and social relationships had declined. Her previous follow-ups noted that she had complete insight into her diagnosis, with a Yale-Brown Obsessive Compulsive Scale score of 27, indicating that she was suffering from severe symptoms. She initially benefited from 200 mg/day of fluvoxamine, experiencing remission, but 15 mg/day of mirtazapine was added to her treatment

due to sleeping difficulties and appetite loss. Subsequently, the severity of her OCD symptoms worsened, leading to an increase in her fluvoxamine dose to 300 mg/day. Before her recent emergency department admission, the patient, feeling overwhelmed by her obsessive thoughts, deliberately ingested 1,500 mg of fluvoxamine, believing it might help alleviate her distressing obsessions. She later expressed regret for her actions, clarifying that the overdose was not an attempt at self-harm or suicide but rather a misguided attempt to silence her intrusive thoughts. She denied any previous history of suicide attempts or self-harm and was not diagnosed with any other medical conditions. She was not taking any proconvulsant drugs and had never previously experienced a seizure. Her history of head trauma was negative.

To restructure her treatment plan, hospitalization in the psychiatry ward was recommended; however, the patient and her family declined inpatient treatment. Although the patient stated that she had no intention of self-harm, the potential for self-harm was considered and explained due to her false beliefs and intrusive thoughts under stress. After a 1-week medication-free period following the intentional overdose, an outpatient clinic appointment was scheduled to develop new treatment strategies for her OCD, and she was discharged from emergency department. A joint follow-up plan with the neurology department was also arranged to ensure seizure prevention and guide future pharmacotherapy. The continuation of levetiracetam as maintenance therapy, regular neurological assessments, and the avoidance of psychotropic agents with potential proconvulsant effects were emphasized in the therapeutic plan. Informed consent was obtained from the patient before the writing and publication of this case study.

DISCUSSION

Although seizures have been considered infrequent adverse effects for various pharmacological agents, they are clinical conditions that can be associated with serious morbidity, require emergency intervention, and have high mortality rates.⁷ Additionally, they can expose individuals to physical trauma and accidents, lead to cerebrovascular events, and compromise airway safety with conditions such as aspiration pneumonia and respiratory arrest.⁷ Therefore, this issue should be carefully assessed

by physicians when considering possible pharmacological treatment choices.

In studies, the frequency of seizures for all psychotropic drugs used at therapeutic doses has been reported to range from 0.1% to 1.5%; in populations with no prior history of seizures, the frequency is reported to be lower, between 0.07% and 0.09%.⁸ Among antidepressants, while some studies associate SSRIs with an increased risk of seizures, other studies suggest that this risk is low and their use is safe even in patients with epilepsy.^{9,10} For fluvoxamine, which belongs to the SSRI group, although Harmant et al¹¹ reported no seizure activity in 35 patients with depression and epilepsy, a few case reports have described seizures at therapeutic doses in patients with a prior history of seizures; Trabert et al³ and Nakahira et al¹² also reported generalized seizures in patients without a previous history who were receiving therapeutic doses of fluvoxamine. In premarketing studies involving patients with OCD, seizures were reported with a frequency of 0.2%.¹³ In cases of fluvoxamine overdose, several reports have described an increased frequency of seizures with severity ranging up to status epilepticus.^{2,6} Overall, seizures represent a recognized but infrequent adverse effect of fluvoxamine, and current data do not allow a clear determination of the underlying mechanism or dose relationship.

Our patient had been followed for a long time with fluvoxamine and mirtazapine treatment without any issues but experienced a witnessed generalized tonic-clonic seizure after a fluvoxamine overdose. Considering that the patient had been using mirtazapine for approximately 3 years without any recent dose changes, it is unlikely that mirtazapine is responsible for the etiology. However, the pharmacodynamic effects of fluvoxamine and drug-drug interactions in cases of polypharmacy cannot be ignored. Fluvoxamine is a potent inhibitor of the CYP1A2 and CYP2C19 cytochrome enzymes and to a lesser extent, the CYP2C9, CYP2D6, and CYP3A4 enzymes.¹⁴ Given that mirtazapine is largely metabolized by the CYP1A2, CYP2D6, and CYP3A4 isoenzymes, an increase in serum levels of mirtazapine would be expected.¹⁵ A review of the literature reveals that evidence regarding the effect of mirtazapine use at therapeutic doses on seizure predisposition is limited to a few reported cases.^{16,17} Additionally, there are intoxication cases in the literature where no seizures were triggered even with overdoses up to 1,350 mg.¹⁸

Both medications used in our case are notable for their serotonergic properties, and considering that the patient's clinical condition developed within hours following the overdose and resolved quickly, serotonin syndrome was also included in our differential diagnoses. Serotonin syndrome is a life-threatening condition often related to serotonin toxicity that develops within hours after exposure to a combination of multiple serotonergic agents or high doses of a serotonergic agent, and seizures can occur in its advanced stages.¹⁹ Symptoms such as nausea and dizziness observed in our patient are also seen in serotonin syndrome.¹⁹ However, during the patient's initial evaluation, clinical data such as normal vital signs, the absence of neurological examination findings like ocular clonus, myoclonus, and hyperreflexia, and not meeting the criteria of the Hunter Serotonin Toxicity Criteria, which is a diagnostic tool for serotonin syndrome, led us to rule out this diagnosis. Additionally, laboratory parameters and brain imaging did not reveal any other causes for the seizure etiology.

After ruling out other causes, the development of seizures related to antidepressant overdose appears to be multifactorial, involving complex changes in neurotransmitter systems. Elevated serotonergic activity may enhance cortical excitability and lower the seizure threshold. Furthermore, imbalances between excitatory glutamatergic and inhibitory GABAergic neurotransmission appear to be critical in seizure development.²⁰ Antidepressants may disrupt GABAergic inhibition or potentiate glutamatergic excitation, promoting neuronal hyperexcitability and seizure initiation. In addition, these agents, at toxic concentrations, can modulate voltage-gated sodium and calcium channels, further contributing to generalized tonic-clonic seizures.²⁰ While the exact mechanisms remain incompletely understood, these neurochemical and electrophysiological changes provide a plausible explanation for seizure occurrence after fluvoxamine overdose.

The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system categorizes the likelihood of a drug causing an adverse event based on timing, alternative causes, and known drug effects.²¹ In this case, the close temporal relationship between fluvoxamine overdose and seizure onset, along with no other identified causes, supports a probable causal link. Therefore, according

to WHO-UMC criteria, this adverse reaction is classified as "probable/likely."

As a limitation, the inability to measure serum drug levels in our case is a constraint due to the limitations of our resources. The dose amount was accepted based on information provided by the patient, and the effects of pharmacokinetic and pharmacodynamic processes following oral intake were disregarded regarding serum drug concentrations. Secondly, pharmacological interactions between mirtazapine and fluvoxamine were interpreted based on existing literature, and it was logically considered that mirtazapine was unlikely to be responsible for the seizure. Lastly, the generalizability of these observations based on a single case is limited, and further research is needed in this regard.

CONCLUSION

Seizures represent a recognized but rare adverse effect of fluvoxamine, particularly in the context of overdose. This case highlights that antidepressant overdose can lead to serious neurological complications, including generalized tonic-clonic seizures, even in individuals without a prior seizure history. Clinicians should remain vigilant to the potential risks associated with overdose of serotonergic agents and other psychotropics and should carefully monitor patients presenting with intentional or accidental ingestion. Early identification and management of seizure activity, continuation of antiepileptic therapy when indicated, and avoidance of psychotropic agents with proconvulsant potential are essential preventive strategies. A multidisciplinary approach involving psychiatry and neurology, along with individualized treatment planning and patient education, can help minimize seizure recurrence and improve overall clinical outcomes.

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