CASE REPORT

Delirium and Pregabalin Use

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Pregabalin has been prescribed during the past decade for diabetic peripheral neuropathy, and some psychiatrists use it off-label to treat anxiety. The most common side effects of pregabalin include dizziness and somnolence, which can often lead to discontinuation of the medication (1). Symptoms of delirium associated with pregabalin, specifically with prominent visual hallucinations, have not been well described in the literature. We present a patient who, after appropriate up-titration of pregabalin in an inpatient hospital setting, experienced delirium with prominent visual hallucinations, which resolved after prompt discontinuation of pregabalin.

CASE

"Mr. J" is a 60-year-old male with a past medical history of type 2 diabetes mellitus with peripheral neuropathy, hyperlipidemia, and depression who was admitted for long-term antibiotic management of a right diabetic foot ulcer with acute osteomyelitis and pathologic fracture. Wound cultures grew extended-spectrum beta-lactamases, staphylococcus epidermidis, and viridans streptococcus. Mr. J was started on intravenous ertapenem for 6 weeks and continued on his home medications of metformin and atorvastatin.

During this hospitalization, Mr. J's infection continued to heal, and he remained otherwise stable with no medication changes. However, he reported burning and tingling pain in his feet, which made it difficult for him to ambulate. Mr. J was started on pregabalin 50 mg three times daily for diabetic peripheral neuropathy. This was continued for 3 days, but he reported no improvement in his symptoms. Pregabalin was increased to 75 mg three times daily and continued for another 3 days. He reported that the burning sensation in his feet improved mildly, and he was able to walk without significant pain, but the pain was still present and bothersome. Pregabalin was subsequently increased to 100 mg three times daily, which he received for another 5 days. With this increased dose, he reported a major reduction in the burning sensation in his feet. However, he also reported new-onset dizziness while getting out of bed. Orthostatic vital signs indicated possible hypovolemia, and Mr. J was encouraged to maintain adequate fluid intake.

On the fifth day of receiving pregabalin 100 mg three times daily, he began reporting frightening visual hallucinations and had one episode of mild agitation in which he was found out of his room and disrupting activity in the hallways. He did not sleep that night or the following day. Mr. J reported seeing a crying girl in his room, who disappeared when he attempted to hug her.

On examination, Mr. J was alert but not oriented to himself, time, or place. There were no other focal deficits on physical or neurological examination. His labs (including white blood cell count) were within normal limits, and his foot infection was improving. A noncontrast head computerized tomography showed no acute intracranial process. Electroencephalography was considered but was not available at the hospital and thus was not performed. At this time, the decision was made to stop pregabalin because of possible cognitive side effects and concern for delirium. Mr. J received haloperidol as needed for severe agitation and was placed on delirium precautions. That evening, he continued to experience worsening disturbing and frightening hallucinations but no agitation. He reported seeing ten children peeking at him through the doors in his room and standing around his bed. He was oriented to himself but not to time or place.

For the next 3 days, Mr. J's mentation appeared to fluctuate, but he consistently reported continued frightening, disturbing visual hallucinations and remained disoriented to place, date, and situation. Cognitive testing was attempted but unable to be performed because the severity of his perceptual disturbances affected his ability to cooperate with such testing. The third day after pregabalin was stopped, Mr. J's delirium resolved and he was oriented to himself, time, and place. He had no other episodes of visual hallucinations or disorientation for the remainder of his hospitalization.

DISCUSSION

Pregabalin is a structural analog of GABA (gamma-aminobutyric acid) that binds at the alpha-2 delta subunit of voltage-sensitive calcium channels, reducing calcium influx (2). Known neurological side effects of pregabalin include dizziness, somnolence, neuropathy, ataxia, vertigo, confusion, euphoria, incoordination, cognitive impairments, tremor, abnormal gait, amnesia, and nervousness (1). Auditory and visual hallucinations have not been identified as adverse effects in the drug label information, nor were these side effects reported in the drug's clinical trials. Cognitive effects of pregabalin have not been well reported in the literature. However, one double-blind, placebo-controlled trial reported that pregabalin used at therapeutic doses had negative effects on cognition as measured by standard cognitive measures (3).

Disturbance in perception (hallucinations) associated with pregabalin use has been reported in a few case reports (4). One report described a 44-year-old female who was started on prega-

KEY POINTS/CLINICAL PEARLS

- Pregabalin is a structural analog of GABA (gamma-aminobutyric acid) that binds to the alpha-2 delta subunit of voltage-sensitive calcium channels, reducing calcium influx.
- Even when pregabalin is titrated up slowly and appropriately, some patients can develop cognitive side effects, such as delirium, which may resolve spontaneously with cessation of the drug.
- Patients prescribed pregabalin should be alerted to the potential for deleterious cognitive side effects of the drug.

balin 600 mg three times daily rapidly and without any titration, who experienced visual hallucinations associated with EEG changes (generalized slowing, with epileptiform discharges in both posterior head regions), which resolved completely after discontinuation of pregabalin and administration of benzodiazepines (5). Another case report described a 44-year-old female started on pregabalin for neuropathic pain, who experienced delirium with prominent visual hallucinations 3 days after the dose was increased, which resolved after discontinuation of pregabalin (6).

The patient described in this case report was admitted to the hospital for several weeks for intravenous antibiotic treatment of osteomyelitis. He had remained stable on his antibiotic regimen along with metformin and atorvastatin (which he had been taking for several years prior to this admission). He was started on pregabalin for diabetic peripheral neuropathy and was noted to have disorientation and prominent visual hallucinations 12 days after pregabalin was initiated and dose-titrated up appropriately and gradually in an inpatient hospital setting. His labs and testing were normal, and his foot infection was shown to be improving. An EEG would have been helpful to obtain in this patient; however, this patient was admitted in a rural hospital without EEG capabilities. The patient's symptoms resolved 3 days after discontinuation of the drug.

DSM-5 criteria for delirium are listed below (6, pp. 596–598):

A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).

B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).

D. Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to an illicit drug or to a medication), or exposure to a toxin, or is due to multiple etiologies.

The patient in this case report exhibited several signs and symptoms of delirium as described in DSM-5, specifically disturbance in awareness and cognition, along with disturbances in perception (hallucinations). This patient's delirium lasted several days before he experienced complete resolution of his symptoms. Because of the temporal relationship seen with cessation of pregabalin and resolution of his symptoms of delirium and lack of other physical examination, laboratory findings, and medication changes, suggesting an alternative cause or diagnosis, we believe that this patient may have experienced delirium secondary to pregabalin use.

Clinicians should be aware of the cognitive side effects of pregabalin, and the potential for patients to develop delirium with visual hallucinations while taking pregabalin, even at therapeutic doses administered in a hospital setting.

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The author has confirmed that details of the case have been disguised to protect patient privacy.

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