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When Lorazepam Worsens Delirium in Your Catatonic Patient

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There is little research about the overlap and treatment of catatonia and delirium. Currently, the *DSM-5-TR* does not acknowledge the potential overlap of these conditions in the clinical setting.[1] Lorazepam, which is the standard of care for catatonia, can worsen delirium, especially in the elderly. Some studies have found that between 12.7% and 30.2% of patients with delirium have catatonia, and patients with delirium often have catatonic symptoms such as negativism, mutism, or stupor, with a variance of symptoms between 8.3% and 72.7%.[2] Studies examining electroencephalography (EEG) obtained during catatonia report abnormalities, such as generalized slowing, which is suggestive of delirium in up to 23% of cases wherein catatonia is thought to be due to psychiatric cause.[3]

Although there is an algorithm highlighting the next steps when benzodiazepines are ineffective in catatonia, no guidelines exist on next steps when lorazepam worsens delirium, even while being effective for catatonia.[4] A recommendation exists that posits glutamate antagonists might be considered in cases of comorbid catatonia with delirium, in which the use of benzodiazepines may worsen delirium.[4] Here we present 2 cases detailing effective alternative strategies in treating co-occurring catatonia and delirium.

Case 1

A 77-year-old woman with a psychiatric history of obsessive-compulsive disorder (OCD), generalized anxiety disorder, and major depressive disorder presented in February 2022 with symptoms indicative of catatonia. Her initial evaluation in the emergency department (ED) revealed various catatonic features, including a positive Mitgehen sign, mutism, stereotypy, waxy flexibility, ambitendency, negativism, withdrawal, stupor, and positive grasp reflex with a Bush-Francis Catatonia Rating Scale[5] (BFCRS) score of 20. There were no signs of delirium, and her laboratory test results showed no significant abnormalities.

According to her family, she had been experiencing worsening depression for approximately 2 months leading up to this episode. Given the high suspicion of catatonia, a lorazepam challenge of 0.5 mg intravenously (IV) was administered, resulting in the resolution of her mutism and Mitgehen sign within 30 minutes, lowering her BFCRS score to 15. Considering her age and the risk of delirium with improvement on lorazepam challenge, she was initiated on 0.5 mg lorazepam by mouth twice daily. Subsequently, her symptoms of ambitendency, withdrawal, stupor, stereotypy, negativism, waxy flexibility, and grasp reflex resolved, significantly improving her BFCRS score to 1.

On the second day, she exhibited delirium including deficits in delayed recall and attention, intermittent agitation, disorientation, and confusion. In response to these developments, the family requested a 24-hour pause in scheduled lorazepam administration. Unfortunately, during this period, the patient's catatonia worsened with the emergence of stupor, facial grimacing, verbigeration, rigidity, and perseveration, resulting in a BFCRS score of 8.

The patient was switched to oral clonazepam 0.5 mg twice daily, and after 24 hours on the new regimen, she experienced worsening delirium and increased symptoms of catatonia, with new-onset posturing and automatic obedience, increased grimacing, stereotypy, negativism, withdrawal, Mitgehen, and grasp reflex, culminating in her highest BFCRS score of 21. Given the worsening catatonia despite the use of benzodiazepines, a trial of zolpidem at 5 mg 3 times daily was initiated based on previous case reports documenting effectiveness when a trial of benzodiazepines fails.[6]

After 24 hours on the zolpidem regimen, the patient rapidly returned to her baseline state, with improvements in both delirium and catatonia symptoms, resulting in a BFCRS score of 0. Notably, she was not sedated while on this dose of zolpidem and was the most interactive, reactive, and cheerful she had been during her duration of treatment in the hospital. The family observed her returning to her baseline condition, which she maintained until her discharge 4 days after symptom resolution.

Case 2

A 74-year-old man with a history of posttraumatic stress disorder presented to the ED with catatonic features. According to his wife, he had been psychiatrically stable until developing bizarre behavior 2 to 3 days before his ED visit, with no apparent stressor. He exhibited prominent stereotypy, mutism, stupor, posturing, grimacing, verbigeration, negativism, withdrawal, and impulsivity, scoring 19 on the BFCRS.

Delirium and medical abnormalities were ruled out, and a 2-mg IV challenge increased spontaneous speech and resolved posturing and stereotypy within 30 minutes, improving his BFCRS score to 12. Lorazepam 1 mg IV 3 times daily was started and titrated to a total daily dosage of 9 mg, yielding only a slight improvement on the BFCRS to 10 by day 3. Concerns arose about delirium superimposed on catatonia, with noted fluctuations in consciousness, hallucinations, intermittent agitation, and cognitive and attention deficits. Reduction of lorazepam led to worsening delirium and catatonia.

By the sixth day, the patient required a nasogastric tube to minimize his aspiration risk due to withdrawal, as well as decreased arousal and consciousness. His BFCRS score increased to15 on day 7 and then 17 on day 8. Given his deterioration, electroconvulsive therapy (ECT) was initiated on day 9 due to documented efficacy of ECT when lorazepam fails.

After the first ECT treatment, his BFCRS score decreased from 17 to 12 within 1.5 hours. Memantine 5 mg nightly was added to enhance the ECT effect, since glutamate antagonists aid in resolution of catatonic symptoms on their own and in combination with other treatments.[7] Lorazepam was tapered to a daily total of 3 mg, and a second ECT treatment was performed. The delirium and catatonia improved, with BFCRS scores of 1 and 0 the following day. On day 13, the nasogastric tube was removed, a final ECT treatment was performed, and the patient returned to his cognitive baseline. Lorazepam was fully tapered off, while memantine was continued daily. The patient remained symptom free during his hospitalization and follow-up with psychiatry 2 weeks later, requiring nothing further than the 3 ECT treatments.

Discussion

Currently, lorazepam is considered the gold standard treatment for catatonia. However, in both cases, while lorazepam initially improved catatonic symptoms, it seemed to contribute to the development of delirium symptoms and a decline in functional status. This prompted us to explore alternative treatments, considering that there were no other significant medical factors contributing to delirium except for hospitalization, age, and benzodiazepine use. We found 2 alternative treatments, zolpidem and ECT combined with memantine, to be remarkably effective in resolving catatonia with co-occurring delirium in both cases.

In the first case, we opted to trial zolpidem, as there have been reports of its success in resolving catatonic symptoms when benzodiazepines fail.[8,9] This decision was influenced by the fact that symptoms emerged on the weekend when ECT was unavailable. Zolpidem binds to the α-1 subunit of the γ-aminobutyric acid-α (GABA-A) receptor, while lorazepam binds non-preferentially to multiple subunits of the receptor. Given zolpidem's short half-life, preferential binding, and documented evidence that mutism is a prognostic factor for poor response on lorazepam, the cost-benefit ratio was in favor of a zolpidem trial.[6] The patient tolerated zolpidem well, likely due to its differential GABA-A receptor binding compared to benzodiazepines.

In the second case, ECT was the preferred alternative treatment because of its rapid treatment of symptoms and due to the patient's significant withdrawal from food and water intake, coupled with marked alternations in consciousness. We also introduced memantine to his treatment regimen to expedite symptomatic treatment, supported by case reports suggesting memantine alone can resolve catatonic symptoms and literature documenting the effectiveness of the glutamate antagonists for ECT-resistant catatonia.[6,10]

There is a scarcity of robust research on the co-occurrence of delirium and catatonia, likely due to overlap of diagnostic criteria that can be challenging for practitioners to differentiate. However, in our cases, both patients exhibited distinct features of catatonia (posturing, stereotypy, Mitgehen) and delirium (perceptual disturbances, altered consciousness, and fluctuating course), making it feasible to establish separate diagnoses for each condition.

While lorazepam remains highly effective for catatonia, caution is warranted, especially in elderly patients with medical comorbidities, as benzodiazepines can exacerbate delirium. While it is likely that lorazepam lowered the treatment threshold for alternative treatments, our patients' risk factors for delirium were their age, benzodiazepine use, and hospitalization, thus providers should promptly consider alternative catatonia treatments if delirium is suspected. Delaying appropriate treatments can prolong hospital stays and lead to additional medical procedures and complications. In our cases, transitioning to alternative catatonia treatments resulted in rapid recovery from both catatonia and delirium within 24–48 hours.

ECT, zolpidem, and glutamate antagonists like memantine and amantadine as adjuncts to ECT are among the best-documented second-line therapies when benzodiazepines precipitate delirium in catatonia patients.[6] Nevertheless, larger prospective studies are needed to further validate neuropsychiatric medication effectiveness in catatonia.

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