COVID-19–Associated Benzodiazepine-Resistant Catatonia Responds to Amantadine

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As of August 2022, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed over 6.4 million lives worldwide.[1] There has been a growing number of reports of the akinetic variant of catatonia in patients with SARS-CoV-2 infection,[2] exceeding all other viral infections. The objective of this case report is to discuss the successful use of amantadine that resulted in the remission of benzodiazepine-resistant catatonia associated with COVID-19 infection. This case is important given the lack of research on preferred treatments of catatonia in the setting of COVID-19 infection.

Case Report

Mr A is a 20-year-old Black man with a history of autism spectrum disorder (ASD), major depressive disorder (MDD), and generalized anxiety disorder (GAD), but no medical conditions, who presented to Cooper University Hospital (CUH) with altered mental status. At baseline, he was found to be independent and employed and had graduated high school with special education classes. Approximately a week before admission to CUH, he was evaluated at his local emergency department (ED) for seizure-like episodes, abdominal pain, and anosmia. He tested positive for SARS-CoV-2 via nasopharyngeal polymerase chain reaction. Although the patient was uncooperative with electroencephalogram (EEG) studies, the neurology team had a low suspicion for seizures and suspected a psychiatric etiology. He was discharged after 3 days to be treated with levetiracetam 500 mg oral daily with an outpatient follow-up epilepsy evaluation, EEG, and magnetic resonance imaging (MRI). Three days later, the patient started to develop signs and symptoms of catatonia and returned to his local ED for worsening agitation. His behavior fluctuated between unresponsive staring episodes and worsening agitation. A non-contrast head computed tomography scan, chest x-ray, and MRI were within normal limits. The neurology consultation found his presentation inconsistent with epilepsy. Mr A was transferred to CUH for further evaluation.

The patient's initial psychiatric examination yielded a 23-item Bush Francis Catatonia Rating Scale[3] (BFCRS) score of 11, positive for stupor, mutism, staring, catalepsy, rigidity, negativism, and withdrawal. He was nonverbal, unable to follow commands, and presented with a restricted affect. The patient's physical and neurologic examinations were unremarkable. The EEG showed no epileptiform abnormalities or seizures.

The neurology team's impression of Mr A's condition was highly suspicious for catatonia with a low suspicion for a primary neurologic pathology. Intravenous lorazepam 1 mg was administered with subsequent improvement in mutism and rigidity. During the mental status examination, the patient was calm, cooperative, and grossly oriented. He continued to show intermittent speech latency and residual signs of confusion regarding his condition. He denied symptoms of depression, mania, and psychosis but was found to have intermittent anxiety over the past few weeks. The initial psychiatric impression was unspecified catatonia, given the patient's treatment response and overt signs of negativism and catalepsy. We also considered other possible etiologies, including post-COVID-19 encephalitis, akinetic mutism, mood disorder with psychotic features, and delirium. The majority of Mr A's diagnostic imaging studies and laboratory work (including blood cultures, lumbar puncture, and inflammatory markers) were within normal limits.

Mr A stayed at CUH for 9.5 weeks with a hospital course complicated by benzodiazepine-resistant catatonia, requiring multiple pharmacologic interventions. His daily BFCRS scores are shown in Table 1. He initially improved with lorazepam 1 mg intravenous (IV) every 8 hours, but over weeks 2 to 4, he would often fluctuate between stuporous and excited catatonic states. He was unable to receive electroconvulsive therapy (ECT). As shown in Table 1, Mr A attained remission in week 5 only after treatment with amantadine, an *N*-methyl-D-aspartate (NMDA) antagonist and dopamine reuptake inhibitor. There were no reported side effects or signs of intolerance with the addition of amantadine, including nausea, dizziness, and insomnia. Overall, his symptoms showed a fluctuating decline based on BFCRS scores. Lorazepam was increased from 1 mg IV 3

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Table 1. Medication Titration During the Hospital Course[a]

Timeline	BFCRS Score	Medications	Intervention
Week 1	11	Lorazepam challenge 1 mg IV Lorazepam 1 mg IV every 8 hours	Add aripiprazole 2.5 mg PO daily
Week 2	2	Lorazepam 1 mg IV every 8 hours Aripiprazole 2.5 mg PO daily	Aripiprazole discontinued on HD 12 Increase lorazepam 1 mg IV every 6 hours
Week 3	6	Lorazepam 1 mg IV every 6 hours	Increase lorazepam 2 mg IV every 6 hours
Week 4	11	Lorazepam 2 mg IV every 6 hours	Increase lorazepam 4 mg IV every 6 hours
Week 5	21	Lorazepam 4 mg IV every 6 hours	Increase lorazepam 5 mg IV every 6 hours Add amantadine 100 mg PO twice daily
Week 6	9	Lorazepam 5 mg IV every 6 hours Amantadine 100 mg PO twice daily	Increase lorazepam 6 mg IV every 6 hours
Week 7	7	Lorazepam 6 mg IV every 6 hours Amantadine 100 mg PO twice daily Diphenhydramine 25 mg IV as needed for agitation (used once)	
Week 8	15	Lorazepam 6 mg IV every 6 hours Amantadine 100 mg PO twice daily	Increase lorazepam 6.5 mg IV every 6 hours
Week 9	6	Lorazepam 6.5 mg IV every 6 hours Amantadine 100 mg PO twice daily	Transition/increase lorazepam 9 mg PO every 6 hours
Week 9.5 Discharge	0	Lorazepam 9 mg PO every 8 hours Amantadine 100 mg PO twice daily	Psychiatry outpatient follow-up with lorazepam taper

[a]Mr A stayed at our hospital for 67 days (9.5 weeks). His initial psychiatric evaluation yielded a BFCRS score of 11, which initially improved with lorazepam 1 mg IV every 8 hours. On HD 9 (week 2), aripiprazole 2.5 mg PO daily was started as an adjunctive treatment for catatonia but was discontinued on HD 12 at his mother's request, as it did not show meaningful improvement. In the first 4 weeks, his condition fluctuated and ultimately worsened with a BFCRS score of 21 on HD 29. He slowly attained remission only after the addition of amantadine 100 mg PO twice daily on HD 30 (week 5), along with lorazepam 5 mg IV every 6 hours (total: 20 mg daily). Throughout the hospital admission, IV lorazepam was increased steadily from 2 mg 3 times daily to a maximum of 9 mg PO 3 times daily (27 mg daily), which was suggestive of benzodiazepine-resistant catatonia. By HD 57, he showed recovery of his catatonia symptoms with BFCRS scores of 0. He was discharged on HD 67 (week 9) on a regimen of lorazepam 9 mg PO every 8 hours and amantadine 100 mg PO twice daily. ECT was recommended in week 6; however, the patient did not undergo ECT due to his involuntary status and issues obtaining consent. It is also important to note that while the BFCRS is the best-studied catatonia rating scale, it lacks uniformity in its reference definitions. It is useful for measuring treatment response, but residual signs may persist even after clinical improvement.

Abbreviations: BFCRS = Bush-Francis Catatonia Rating Scale, ECT = electroconvulsive therapy, HD = hospital day, IV = intravenous, PO = oral.

times daily to a maximum of 9 mg 3 times oral daily (27 mg daily). The final regimen at discharge was amantadine 100 mg oral twice daily and lorazepam 9 mg oral 3 times daily, which proved to be the best intervention for his catatonia. We did not taper lorazepam during Mr A's hospital stay due to his complicated course of catatonia. His functioning improved with cognitive rehabilitation, occupational/speech therapy, and outpatient psychiatry follow-up. The outpatient psychiatry team tapered his lorazepam over several months. Mr A continues his recovery from catatonia and has returned to his baseline mental status and favorite activity of playing basketball.

Discussion

This case is unique, as it provides a discussion of treatment strategies for benzodiazepine-resistant catatonia associated with COVID-19 infection. While there is a possibility that SARS-CoV-2 may have contributed to the catatonia symptoms in this patient, it is important to recognize his past psychiatric diagnoses (ASD, MDD, GAD) as risk factors. The mechanisms underlying COVID-19 infection and catatonia are still yet to be elucidated, but inflammatory, stress, and psychological factors have been proposed.[2] The current literature studying COVID-19 and catatonia is mostly limited to case reports, with a heterogeneity of clinical presentations. Lorazepam was successfully used in 18 patients, who demonstrated notable improvements in core symptoms of catatonia, including mutism, echolalia, rigidity, and waxy flexibility.[4] ECT was also effective in 4 patients.[4] This finding is consistent with previous literature supporting lorazepam and ECT as effective first-line treatments, particularly in acute catatonia, irrespective of the cause.[5] However, there is a lack of studies on other potential treatments for benzodiazepine-resistant catatonia associated with COVID-19 infection. In a naturalistic study[6] of 66 children and adolescents with catatonia, it was found that benzodiazepines improved catatonia in 65% of cases. It is particularly important for clinicians to be aware of other potential treatments (eg, ECT, amantadine), as it has been shown that approximately 30% to 35% of cases do not respond to benzodiazepines.[6] Thus, there is a need for research on the possible etiopathogenetic role of SARS-CoV-2 in catatonia that may inform novel therapeutics for this rapidly emerging health condition.

When catatonia fails to respond to increasing doses of lorazepam, as we saw in this patient's case, we suggest considering the use of an oral NMDA antagonist (eg, amantadine, memantine), especially when ECT is unavailable. Other NMDA antagonists include dextromethorphan/

quinidine[7] and minocycline.[8] This is consistent with previous literature demonstrating the successful use of oral amantadine in benzodiazepine-resistant pediatric catatonia, suggesting the importance of glutamatergic/NMDA hyperactivity in the development of catatonia symptoms.[9] We recommend a starting dose of amantadine of 100 mg oral daily, which can be titrated by 100 mg every 3 to 4 days to a total dosage of 600 mg daily in divided doses. Memantine can alternatively be used starting at 10 mg oral daily to a total dosage of 20 mg daily. Amantadine can be used as monotherapy or in combination with benzodiazepines.[10] It is generally well tolerated, as seen in our patient, with the most commonly reported side effects being nausea, dizziness, and insomnia (5%–10% incidence).[11]

This is the first case report, to our knowledge, highlighting the use of amantadine in benzodiazepine-resistant catatonia associated with COVID-19 infection. The combination of amantadine and lorazepam was safe, effective, and tolerable and may be a useful approach in managing COVID-19–associated catatonia resistant to benzodiazepines. As the pandemic persists, we hope to bring our community's attention to COVID-19–associated catatonia and the use of amantadine in benzodiazepine-resistant catatonia.

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