mhc
MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Memantine leading to physical aggression in the treatment of chronic catatonia secondary to schizophrenia: A case report

Andrew Chantha Hean, PharmD[1]; Jessica Jones, PharmD[2]; Michael Arena, MD[3]; Kevin Kavanagh, PharmD[4]

How to cite: Hean AC, Jones J, Arena M, Kavanagh K. Memantine leading to physical aggression in the treatment of chronic catatonia secondary to schizophrenia: a case report. Ment Health Clin [Internet]. 2025;15(4):218-21. DOI: 10.9740/mhc.2025.08.218.

Submitted for Publication: June 13, 2024; **Accepted for Publication:** April 24, 2025

Abstract

Introduction: Memantine is a noncompetitive N-methyl-D-aspartate receptor antagonist approved by the FDA for moderate to severe Alzheimer's dementia. Memantine is also recommended as an off-label treatment in current catatonia clinical guidelines when benzodiazepines alone are inadequate.

Case: A 37-year-old male with a history of schizophrenia on psychiatric conservatorship, stimulant use disorder, and traumatic brain injury was stabilized on risperidone 4 mg twice daily, diphenhydramine 50 mg twice daily, divalproex delayed release 500 mg twice daily, and lorazepam 1 mg twice daily for catatonia. Lorazepam was titrated for unresolved chronic catatonic symptoms but was not tolerated beyond 5 mg total per day due to hemodynamic instability. Owing to barriers in initiating clozapine or electroconvulsive therapy, the patient was started on memantine to address residual catatonia symptoms. After the addition of memantine, the patient began to spontaneously speak in multiple languages and engage in discharge planning, but shortly after a dose increase to 15 mg daily also displayed increased aggressive behaviors. The aggression improved after decreasing the dose to 10 mg daily, and the patient was discharged.

Conclusions: This case adds to the body of evidence for memantine in catatonia with underlying schizophrenia and, to our knowledge, is the first described case of memantine uncovering aggression during catatonia treatment.

Keywords: memantine, catatonia, benzodiazepine, refractory, schizophrenia

[1] (Corresponding author) Assistant Professor of Pharmacy Practice and Administration, Western University of Health Sciences, College of Pharmacy, Pomona, California, ahean@westernu.edu, ORCID: https://orcid.org/0000-0002-8340-2296; [2] Behavioral Health Pharmacy Specialist, Department of Pharmacy, Sharp Grossmont Hospital, San Diego, California, ORCID: https://orcid.org/0000-0002-6002-7219; [3] Attending Psychiatrist, San Diego County Psychiatric Hospital, County of San Diego Health and Human Services Agency, San Diego, California, ORCID: https://orcid.org/0009-0005-4979-0554; [4] Clinical Pharmacist, San Diego County Psychiatric Hospital, County of San Diego Health and Human Services Agency, San Diego, California, ORCID: https://orcid.org/0000-0002-9359-9790

Disclosures: The authors have no conflicts of interest to disclose.

Introduction

Although the gold standard for catatonia treatment is considered to be benzodiazepines, some patients are partial or nonresponders at adequate doses, necessitating alternative or adjunct treatments.[1] Given that the N-methyl-D-aspartate receptor (NMDAR) may be dysfunctional in patients with catatonia, leading to a loss of GABA-A and dopamine activity, NMDAR antagonists have been proposed as an alternative catatonia treatment.[1] Memantine is a noncompetitive NMDAR antagonist approved by the FDA for moderate to severe Alzheimer's dementia.[2] However, it has been recently recommended as an off-label treatment in catatonia when benzodiazepines are inadequate by the 2023 British Association for Psychopharmacology Catatonia Guidelines and the 2018 Academy of Consultation-Liaison Psychiatry's Evidence-Based Medicine Subcommittee Monograph on Catatonia.[3,4] Current evidence supporting these recommendations is limited to case reports, and adverse effects of this indication are poorly described in the literature. In this case, we describe

the use of memantine to address a patient's catatonia, resulting in an increase in cognition but also increased episodes of physical aggression.

Case Report

A 37-year-old Somali male with a history of schizophrenia on psychiatric conservatorship, stimulant use disorder, and traumatic brain injury was admitted to the inpatient psychiatric unit on a legal hold by police due to physical aggression involving striking his case worker and not eating for multiple days at his board and care facility. The initial evaluation was positive for mutism, negativism, agitation, and stupor. The admission labs and urine drug screen were unremarkable. The patient stopped all medications after prior hospital discharge 2 weeks before presentation. Of note is that no rating scale assessment was performed for catatonia at this time.

On hospital day 2, he was restarted on the medication regimen recommended upon most recent discharge. This consisted of risperidone 4 mg BID for psychosis, diphenhydramine 50 mg BID for extrapyramidal symptom prophylaxis, divalproex delayed release 500 mg BID for mood lability, and a new regimen of lorazepam 1 mg BID for catatonia. By hospital day 4, the patient was noted to be more reality-oriented without any episodes of physical aggression. Lorazepam was titrated for unresolved catatonic symptoms over 24 days, reaching a dose of 5 mg per day split into 3 doses. However, after 2 days, this was titrated back to 1 mg BID due to concerns about the patient's average systolic blood pressure decreasing to a range of 90 to 100 mm Hg during titration. The patient was noted to have minimal improvements in catatonia at these doses.

For the remaining hospital admission, the patient's maintenance medications were not modified further as his outpatient team endorsed that he appeared to be at his baseline. The patient remained admitted to complete discharge disposition to a lower-level care facility. Throughout this time, the patient would intermittently refuse to eat or drink but only in 1 instance required intramuscular olanzapine due to medication refusal. The patient refused blood draws needed for clozapine during this period, and the team chose not to pursue involuntary electroconvulsive therapy. Otherwise, the patient's catatonia symptoms continued to include periodic stupor, mutism, and waxy flexibility. During this period, the patient was also found to have a tooth abscess but continually refused oral antibiotics offered to him.

On hospital day 107, memantine 5 mg daily was initiated following the clinical pharmacy team's recommendation to address remaining catatonia symptoms. Over the next 2 days, eye contact increased, waxy flexibility decreased, and the patient spontaneously spoke English for the first time during the encounter and began to ask about his discharge disposition. On hospital day 112, the patient's social worker, who was fluent in Dutch, confirmed that the patient spontaneously began to converse in Dutch with them. The patient endorsed his fluency, which aligned with his prior social history.

On hospital day 114, the patient began to accept antibiotics for their tooth abscess and completed the full 10-day course. The dose of memantine was then increased to 10 mg daily, and on hospital day 121 was increased to 15 mg daily. Approximately 12 hours after receiving the first 15 mg dose of memantine, the patient charged out of his room while yelling in a foreign language and punching walls, triggering a behavioral code necessitating 4-point restraints and involuntary administration of intramuscular medications. Given the patient's prior social history, the patient was assumed to be yelling in Arabic; however, this could not be confirmed. The nursing staff confirmed that this behavioral episode was unprovoked and without known cause. This was the patient's first behavioral code observed throughout the index hospitalization and 3 prior facility admissions. Memantine was subsequently decreased back to 10 mg daily the next day on hospital day 122. On hospital day 134, the patient was observed to be punching his mattress and endorsed auditory hallucinations for the first time during admission. No further behavioral codes or endorsements of hallucinations occurred after this. The patient's overall presentation remained the same, as there were minimal additional improvements in catatonia symptoms after the initial improvement. The patient's mood remained stable as previously in the admission, described only as "good" or "okay" each day. The first Bush-Francis Catatonia Rating Scale assessment during the admission on hospital day 168 resulted in a score of 17, with positive symptoms for immobility/stupor, mutism, staring, posturing/catalepsy, grimacing, manneriisms, and rigidity. On hospital day 170, lorazepam titration was re-trialed for remaining catatonic symptoms. On hospital day 195, the patient's treatment team secured placement at a long-term locked facility. Lorazepam was still being titrated but was not yet noted to have a significant benefit, and catatonia symptoms remained the same overall. However, it was determined the patient was still psychiatrically stable for discharge to a lower level of care. The catatonia discharge regimen included lorazepam 5 mg 3 times daily and memantine 10 mg daily. During lorazepam titration, the team deemed hemodynamics more stable than the first titration attempts earlier in admission. Systolic blood pressure ranged from 95 to 125 mm Hg with a median of 115 mm Hg. Throughout the admission, the patient's risperidone, diphenhydramine, and divalproex delayed release regimens were unchanged (a timeline of key psychiatric medication changes is provided in the Table).

Discussion

From our search, NMDAR antagonists are described in the literature as being used to treat catatonia but are currently based only on case reports and case series.[3] Adverse effects of this

TABLE: Timeline of psychiatric medication changes

Hospital Day	Medication Regimen Change
Day 2	Initial Regimen resumed in hospital: Risperidone 4 mg BID Diphenhydramine 50 mg BID Divalproex DR 500 mg BID Lorazepam 1 mg BID (new, for catatonia symptoms)
Day 26	Lorazepam reaches 5 mg/d total
Day 28	Lorazepam decreased back to 1 mg BID due to hemodynamic concerns
Day 107	Memantine 5 mg daily initiated
Day 114	Memantine increased to 10 mg daily
Day 121	Memantine increased to 15 mg daily, aggression occurs ~12 hr after dose
Day 122	Memantine decreased back to 10 mg daily
Day 170	Lorazepam titration re-trial begins
Day 178	Lorazepam dose reaches 10 mg/d total
Day 195	Discharge regimen: Risperidone 4 mg BID Diphenhydramine 50 mg BID Divalproex DR 500 mg BID Lorazepam 5 mg TID Memantine 10 mg daily

BID = twice daily; DR = delayed release; TID = 3 times daily.
Of note, risperidone, diphenhydramine, and divalproex DR regimens did not change throughout admission. Although lorazepam titration was to be continued at hospital discharge, the patient was considered stable enough for disposition to a lower level of care.

indication are not well described in these reports. Therefore, our case is in alignment with reports of memantine's efficacy in catatonia in patients with underlying schizophrenia. However, to our knowledge, it is the first to describe recurring aggression after memantine is titrated. Prior reports describe the full resolution of catatonia with dose titration or even recurrence of symptoms when memantine was stopped too early.[1] However, ours highlights a case of partial improvement limited by further dose optimization due to an adverse effect.

Of note, prior case report-based reviews show that improvement in catatonia symptoms with NMDAR antagonists generally occurs within a 7-day window after initiation when used as an adjunct to benzodiazepines[3] and that full resolution of catatonia may take months.[1] In our case, initial improvement in symptoms was observed within 2 days. In a review of 12 cases using memantine in catatonia, the mean daily dose was 12.5 mg (SD 6.2).[5] Our patient, in this case, remained within this dosing range.

A Naranjo Adverse Drug Reaction Probability Scale analysis[6] by the authors of this report generates a score of 6, which denotes the "probable" likelihood that memantine caused increased aggression. In particular, the aggression appearing after memantine administration, a lack of alternative causes for the aggression, no recurrence of aggression with nursing staff after decreasing the memantine dose, and objective witnesses to the aggression were all contributors to this score. The peak concentration of memantine is noted to be 3 to 7 hours after oral administration.[2] In our case, the episode of aggression occurred approximately 12 hours post-dose; therefore, pharmacokinetically, an adverse effect from a dose increase of memantine is plausible.

Pharmacodynamically, NMDAR antagonists have been proposed as a treatment in reducing aggression, but some animal studies have documented increased aggression, particularly in times of heightened stress or ethanol consumption.[7,8] A retrospective study of 196 dementia patients treated with memantine for 6 months showed trends toward improvement in agitation but with a small proportion possibly developing treatment-induced agitation.[9] The authors of this study also propose that patients with preexisting low-baseline glutamatergic tone, a part of the glutamate hypothesis model in psychotic disorders, may be more vulnerable to a psychosis and agitation-inducing effect of NMDAR antagonists, which would explain this paradoxical effect.[9] In our case, there may have been a combination of improvement in the patient's catatonia and improved insight, as well as a medication-induced effect, that led to increased aggression.

NMDAR antagonists have been proposed as adjunctive treatments for negative symptoms in schizophrenia.[10] In our case, it is unclear to what extent memantine improved catatonic-like negative symptoms of schizophrenia rather than catatonia as a distinct phenomenon itself, given the chronic nature of the patient's catatonia symptoms. Furthermore, we could not access any outside records to follow up on the patient's response to memantine or lorazepam after hospital discharge.

When initiating memantine for catatonia, we recommend patients be monitored closely for a return in physical aggression or positive schizophrenia symptoms if these were preexisting. Future literature should address treatment strategies to target such symptoms without the need to withdraw NMDAR antagonist treatment for catatonia. In this case, lorazepam remained at a low dose from a prior benzodiazepine trial while memantine was being titrated, but it may be possible that the combination of a higher dose of lorazepam with memantine also would have also prevented such physical aggression from re-manifesting.

Conclusion

Clinicians and future researchers should consider memantine as a treatment option when benzodiazepines do not adequately resolve chronic catatonia symptoms. Clinicians should be vigilant regarding the recurrence of physical aggression and positive symptoms of schizophrenia following memantine initiation for catatonia.

References

1. Beach SR, Gomez-Bernal F, Huffman JC, Fricchione GL. Alternative treatment strategies for catatonia: a systematic review. Gen Hosp Psychiatry. 2017;48:1-19. DOI: 10.1016/j.genhosppsych.2017.06.011
2. Namenda (memantine hydrochloride). Package insert. Allergan USA, Inc; 2018.
3. Rogers JP, Oldham MA, Fricchione G, Northoff G, Wilson JE, Mann SC, et al. Evidence-based consensus guidelines for the management of catatonia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol (Oxf). 2023;37(4):327-69. DOI: 10.1177/02698811231158232
4. Denysenko L, Sica N, Penders TM, Philbrick KL, Walker A, Shaffer S, et al. Catatonia in the medically ill: etiology, diagnosis, and treatment. The Academy of Consultation-Liaison Psychiatry Evidence-Based Medicine Subcommittee Monograph. Ann Clin Psychiatry. 2018;30(2):140-55. PMID: 29697715
5. Theibert HPM, Carroll BT. NMDA antagonists in the treatment of catatonia: A review of case studies from the last 10 years. Gen Hosp Psychiatry. 2018;51:132-3. DOI: 10.1016/j.genhosppsych.2017.10.010
6. Naranjo CA, Busto U, Sellers EM, Sandor O, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. DOI: 10.1038/clpt.1981.154
7. Bartsch CJ, Nordman JC. Promises and pitfalls of NMDA receptor antagonists in treating violent aggression. Front Behav Neurosci. 2022:16:938044. DOI: 10.3389/fnbeh.2022.938044
8. Nordman JC, Bartsch CJ, Li Z. Opposing effects of NMDA receptor antagonists on early life stress-induced aggression in mice. Aggress Behav. 2022;48(3):365-73. DOI: 10.1002/ab.22022
9. Da Re F, Rucci F, Isella V. Retrospective study on agitation provoked by memantine in dementia. J Neuropsychiatry Clin Neurosci. 2015;27(1):e10-3. DOI: 10.1176/appi.neuropsych.13100226
10. Andrade C. Memantine as an augmentation treatment for schizophrenia: limitations of meta-analysis for evidence-based evaluation of research. J Clin Psychiatry. 2017;78(9):e1307-9. DOI: 10.4088/JCP.17f11998