

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Clozapine for the management of persistent catatonia

Karim Tabbane, MD; Soumeyya Halayem, MD; Ridha Joobar, MD, PhD

A 42-year-old man with a diagnosis of undifferentiated schizophrenia has been hospitalized several times since age 23 for psychotic relapses, usually in the context of nonadherence to medication.

During the last relapse, he was concerned about many plots being planned against him for vague reasons. He experienced catatonic symptoms, including rigid postures, resistance to eating and drinking, immobility, mutism and staring, and displayed periods of unexplained aggressiveness. Physical examination revealed waxy flexibility with no extrapyramidal symptoms or fever. He had a score of 24 on the Bush–Francis Catatonia Rating Scale (BFCRS), which is compatible with a severe form of catatonia.

Even in a patient with psychiatric illness, a plethora of medical conditions can be associated with catatonia. This emphasizes the importance of ruling out a somatic cause.^{1,2} The patient was assessed by an internist and a neurologist, and no clinical abnormalities were identified. Laboratory results, including MRIs and electroencephalography (EEG) scans were unremarkable.

Because the patient refused intravenous injections, lorazepam was initiated orally and was rapidly titrated up to 6 mg daily for more than 15 days, without any effect. However, higher doses were not tolerated. Subsequently, the patient accepted intramuscular injections, which resulted in partial and transitory remission of the catatonic symptoms for a few hours. After a gradual discontinuation of benzodiazepines (BZD), electroconvulsive therapy (ECT) was initiated. Two

series of treatments of 20 sessions each with unitemporal followed by bitemporal electrode placement were completed with no significant improvement, and the score on the BFCRS remained between 20 and 24.

Risperidone (4–6mg/d) and aripiprazole (20mg/d) were each used for a period of at least 6 weeks but were not able to alleviate catatonia symptoms. Parkinsonism was systematically assessed and corrected using anticholinergic agents as needed. Finally clozapine was initiated and gradually titrated to 400 mg over a period of 5 weeks. A significant decrease in the BFCRS score (final score of 4) was observed after 5 weeks, allowing for long-deferred care and discharge from the hospital.

In contrast to acute catatonia, chronic catatonia is less responsive to first-line treatments, including lorazepam and ECT, especially in the context of schizophrenia.^{2–7} Using lorazepam for long-term periods has been proposed as a therapeutic option, although the therapeutic response may be slower, taking months rather than days.^{2,4}

It is generally recommended to discontinue antipsychotics (APs) in patients presenting with catatonia, as APs increase parkinsonism, leading to a potential aggravation of catatonia and an increase in the risk of neuroleptic malignant syndrome (NMS).^{2,4,8} However, atypical APs are known to have weak γ -aminobutyric acid (GABA) agonist activity and serotonin (5-HT₂) antagonism that could stimulate dopamine release in the prefrontal cortex and alleviate catatonic symptoms.⁹ In the event that the catatonia does not resolve with either BZDs or ECT in a patient with schizophrenia, it has been recommended to cautiously initiate atypical APs while maintaining the patient on BZDs.^{3,4}

Even though NMS was described in some catatonic patients treated with clozapine,⁸ this medication has been

shown to be more efficient than other APs for the treatment of chronic catatonia with schizophrenia, although most of the studies reported on a small number of cases.^{10–12} In line with the usual recommendation for clozapine initiation, the treatment requires a baseline evaluation, slow titration and close monitoring.¹⁰ A daily dose between 300 and 750 mg may be required to achieve efficacy,^{10,11} and relief from catatonic symptoms is observed within 2–7 weeks of treatment.^{10–12}

The neurobiology of catatonia is complex,^{13–15} and clozapine may be effective through its actions at various biological junctures of this neurobiology.^{10,16} It is possible that the net effect of clozapine on dopamine neurotransmission (low D₂ receptor occupancy coupled with increased dopamine release in the striatum via the stimulation of 5-HT_{1A} receptors) contributes to the anticatatonic effects of clozapine. Also, clozapine could modulate glutamate and GABA neurotransmission.^{13–15} Alternatively, but not exclusively, the effect of clozapine could derive from its enhanced antipsychotic properties.²

Affiliations: From the Faculty of Medicine, Razi Hospital, La Manouba, Tunisia (Tabbane, Halayem); and the Department of Psychiatry, McGill University, Montreal, Que., Canada (Joobar).

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References

1. Sienaert P, Dhossche DM, Vancampfort D, et al. A clinical review of the treatment of catatonia. *Front Psychiatry* 2014;5:181-90.
2. Fink M, Taylor MA, editors. *Catatonia: a clinician's guide to diagnosis and treatment*. New York (NY): Cambridge University Press; 2003.

3. Rosebush PI, Mazurek MF. Pharmacotherapy. In: Caroff SN, Mann SC, Francis A, Fricchione GL, editors. *Catatonia: from psychopathology to neurobiology*. Washington (DC): American Psychiatric Publishing; 2004. p. 141-50.
4. Rosebush PI, Mazurek MF. Catatonia and its treatment. *Schizophr Bull* 2010;36: 239-42.
5. Ungvari GS, Chiu HF, Chow LY, et al. Lorazepam for chronic catatonia: a randomized, double-blind, placebo-controlled cross-over study. *Psychopharmacology (Berl)* 1999;142:393-8.
6. Luchini F, Medda P, Mariani MG, et al. Electroconvulsive therapy in catatonic patients: efficacy and predictors of response. *World J Psychiatry* 2015;5:182-92.
7. Van Waarde JA, Tuerlings JH, Verwey B, et al. Electroconvulsive therapy for catatonia: treatment characteristics and outcomes in 27 patients. *J ECT* 2010;26: 248-52.
8. Paparrigopoulos T, Tzavellas E, Ferentinos P, et al. Catatonia as a risk factor for the development of neuroleptic malignant syndrome. *World J Biol Psychiatry* 2009;10:70-3.
9. Stahl SM, editor. *Stahl's essential psychopharmacology. Neuroscientific basis and practical applications*. 4th Edition. Cambridge (Mass.): Cambridge University Press; 2013.
10. Dursun SM, Hallak JEC, Haddad P, et al. Clozapine monotherapy for catatonic schizophrenia: Should clozapine be the treatment of choice, with catatonia rather than psychosis as the main therapeutic index? *J Psychopharmacol* 2005;19:432-3.
11. Chattopadhyay S, Saha I, Dan A, et al. Clozapine responsive catatonia: a series of five cases. *Ind Psychiatry J* 2012;21:66-8.
12. England ML, Ongur D, Konopaske GT, et al. Catatonia in psychotic patients: clinical features and treatment response. *J Neuropsychiatry Clin Neurosci* 2011;23: 223-6.
13. Melone M, Bragina L, Conti F. Clozapine-induced reduction of glutamate transport in the frontal cortex is not mediated by GLAST and EAAC1. *Mol Psychiatry* 2003;8:12-3.
14. O'Connor WT, O'Shea SD. Clozapine and GABA transmission in schizophrenia disease models: establishing principles to guide treatments. *Pharmacol Ther* 2015;150:47-80.
15. Ellul P, Choucha W. Neurobiological approach of catatonia and treatment perspectives. *Front Psychiatry* 2015;6:182.
16. Wadekar M, Syed S. Clozapine-withdrawal Catatonia. *Psychosomatics* 2010;51:355.