CLOZAPINE WITHDRAWAL INDUCED CATATONIA: A CASE SERIES

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ABSTRACT
Catatonia is a symptom of behavioral and motor disturbance and can occur in several disorders including neurodevelopmental, psychotic, bipolar, depressive disorders and other medical conditions. Catatonia occurring due to clozapine-withdrawal has been documented in the medical literature as case reports.[1,9,10] Prolonged use of clozapine leading to increase in GABA activity and resultant GABA receptor adaptations may result in catatonia after abrupt withdrawal of the clozapine. We are discussing here a case series of two patients who presented with catatonia following the withdrawal of clozapine. These two cases of catatonia improved with the treatment with Lorazepam and Electroconvulsive therapy.

KEYWORDS: Catatonia, Clozapine, Withdrawal, Schizophrenia.

INTRODUCTION
Clozapine is an atypical antipsychotic used in the treatment of Schizophrenia and other psychiatric disorders. It is characterized by its property of blocking multiple receptors like dopamine, muscarinic, serotonergic, histaminic, and adrenergic receptors. Clozapine withdrawal is associated with cholinergic overdrive and gamma-aminobutyric acid (GABA) supersensitivity. Cholinergic overdrive following clozapine withdrawal may result in nausea, vomiting, diarrhea, headache, agitation, confusion, and diaphoresis. These symptoms are probably explained by the antimuscarinic properties of clozapine and appear to respond to anticholinergic treatment. Some patients appear to have worsening of psychosis and / or abnormal movements. More importantly, in very rare instances, clozapine withdrawal has been associated with catatonic symptoms.
We have come across two patients of schizophrenia who were receiving clozapine and developed catatonia after an abrupt stoppage of it. Catatonia was diagnosed using the Diagnostic and Statistical Manual, 5th Edition (DSM-5). These patients were admitted in a psychiatric indoor unit in a tertiary care hospital. They were treated with reinitiation of Clozapine and showed marked improvement in the catatonic symptoms.

**CASE 1**

A 33 years old female suffering from schizophrenia since 15 years, presented with acute onset behavioral disturbances in the form of withdrawn behavior, mutism, staring spells, stiffness in joints, maintaining odd postures and sleep disturbances. She was neither accepting food & water nor taking bath for the past few days. She was brought to the hospital by her mother and was admitted to the indoor psychiatric ward in view of her severity of symptoms.

On mental status examination (MSE), she was ill kempt in appearance, conscious, uncooperative and not communicative. She was having intermittent purposeless movements of her hands with decreased psychomotor activity and increased reaction time. She did not convey her mood and her affect was restricted. She was uncooperative for formal MSE. She had mutism and negativism with reluctance to move around. Her judgment was impaired and insight was lacking. In the ward, she continues to be mute, mostly staying in bed except to use the bathroom. She was not accepting anything orally. Bush-Francis Catatonia Rating Scale (BFCRS) score was 16/69 which indicated a moderate degree of catatonia. She was given a challenge of the Lorazepam and it was positive, confirming the diagnosis of functional catatonia. Her past treatment records suggested that she was taking treatment for Schizophrenia over the last 15 yrs. She was previously admitted in the psychiatry ward many times and was treated with medications and ECTs. Recently she was well maintained on Tab. Clozapine 200 mg/day and Tab. Amisulpride 100 mg/day for the last 4 years. However, a week back before this admission her tab. Clozapine was stopped abruptly and she was shifted on Tab. Quetiapine 100 mg by her treating psychiatrist. Thereafter within the next 2 days she presented to OPD with catatonic symptoms as mentioned above.

Her physical examination and routine laboratory investigations were within normal limits. In view of past good response to clozapine, she was restarted on tablet clozapine with a dose of 25 mg HS, which was gradually uptitrated to 300 mg as per NICE guidelines. Her baseline blood cell counts were within normal limits. In view of the severity of symptoms like refusal to eat food and medicines and self neglect she was started on a course of ECTs
(electroconvulsive therapy) with informed consent from the caregiver. With this line of treatment, she began to accept food and medications orally, her self-care improved and biofunctions were also improved significantly. Her interaction with her mother and therapist improved gradually. BFCRS score decreased to 1 after 3 weeks. She was discharged from the hospital after successful resolution of all her symptoms and was asked to follow up in the OPD after 7 days of discharge.

Case 2
A 20-year-old single female was brought by her parents & has been suffering with schizophrenia for 3 years. She presented with acute onset behavioral disturbances like withdrawn behavior, mutism, staring spells, stiffness in joints, maintaining odd postures for long hours. Her psychomotor activities were retarded. She was admitted to the psychiatry ward in view of catatonic symptoms. The history obtained revealed that she was well maintained on tablet Clozapine 250 mg per day in divided doses. However, she stopped taking the tablet clozapine abruptly around 15 days back due to the non-availability of the tablet as she missed her regular appointment with the psychiatrist. She presented with above mentioned catatonic symptoms within 5 days of sudden withdrawal of clozapine.

On mental status examination (MSE), she was ill kempt, conscious, uncooperative, not communicative with reduced psychomotor activity and increased reaction time. Her mood was not conveyed and affect was restricted in range. She lacked social judgment and insight was absent. In the ward she continues to be mute and not moving with rigid posture. She refused to accept anything orally. Her Bush-Francis Catatonia Rating Scale (BFCRS) score was 18/69 which was indicative of moderate degree of catatonia. After giving the Lorazepam Challenge Test it decreased to 15. In view of past good response to clozapine, tablet clozapine was again reintroduced with a dose of 25 mg HS and gradually uptitrated as per NICE guidelines. All baseline investigations of Clozapine monitoring were kept (Blood pressure, Hemogram, liver function tests, lipid profile, and blood sugar) and no significant side effects were noted. In view of her psychomotor retardation and withdrawn behavior she was subjected to a course of electroconvulsive therapy with due medical fitness and informed consent. With this line of treatment, she showed improvement in her symptoms. Her self-care improved, biofunctions were stabilized, and she began to accept food and medications orally. She started communicating with her parents and other staff in the ward. BFCRS score decreased to 0 at the end of 3 weeks of treatment.
DISCUSSION
Catatonia is a complex clinical syndrome which presents with a wide range of symptoms, primarily of the motor system. It can be caused by several psychiatric, neurological or medical disorders, as well as from the use of certain psychotropic drugs or, as recently illustrated, from the discontinuation of others. Before the 1990s it was thought to be mainly associated with the diagnosis of schizophrenia. However now we know that it can be manifested in the context of a plethora of psychiatric, neurological and medical conditions. The psychiatric disorders most commonly underlying a catatonic syndrome are bipolar disorder, unipolar depression, psychotic disorders and autistic spectrum disorders. According to the DSM 5, the diagnosis of catatonia requires the presence of at least three of the following symptoms: catalepsy, waxy flexibility, mutism, stupor, agitation, negativism, mannerisms, posturing, stereotypies, grimacing, echolalia and echopraxia [DSM]. Given that mutism and stupor are considered to be the core symptoms of the syndrome, clinicians should be attentive to confirm or exclude the diagnosis of catatonia when a patient presents either one of them, regardless of the underlying pathology.

Subtypes of catatonia[4]
1) Retarded type, characterized by the predominance of immobility, mutism, waxy flexibility, negativism, automatic obedience, staring and posturing.
2) Excited type that is associated with severe psychomotor agitation.
3) A third, more severe type, called malignant catatonia, typically presents with autonomic instability, fever, diaphoresis and agitation, has a high mortality rate and has a lot of overlapping symptoms with neuroleptic malignant syndrome, leading researchers to propose a shared pathophysiological mechanism.

Catatonia usually requires prompt treatment in an inpatient care unit, as it could result in severe clinical complications as a result of immobility and withdrawal from eating and drinking. Such complications include malnutrition, dehydration, various infections, deep venous thrombosis and pulmonary embolism, pressure ulcers or muscle contractures.

 Withdrawal symptoms are common upon discontinuation of psychiatric medications. Catatonia, a neuropsychiatric condition proposed to be associated with gamma-aminobutyric acid (GABA) hypoactivity due to its robust response to benzodiazepines, has been described as a withdrawal syndrome in case reports but is not a well-recognized phenomenon.
Benzodiazepines are the first-line treatment for catatonia regardless of the underlying cause\cite{1} with high treatment response rates.\cite{2-5} Benzodiazepines exert their effects on GABA_{A} receptors, which are classified as ligand-gated ion channels. When GABA binds to its binding site on the GABA_{A} receptor, it increases the frequency of opening of the receptor chloride channel, allowing more chloride to pass through, resulting in an inhibitory effect. The flow of ions through the channel also depends on the concentration gradient of the ions and the membrane potential of the cell. Benzodiazepines are classified as a positive allosteric modulator, as they bind to a separate site on the GABA_{A} receptor. Benzodiazepines amplify the effect of GABA on the GABA_{A} receptor by increasing the frequency of opening of the chloride channel more than when GABA alone is present. Benzodiazepines have no activity on their own, and thus require the presence of GABA at the GABA_{A} receptor to exert their effect.\cite{6} The well-established efficacy of benzodiazepines in the treatment of catatonia implicates GABA hypoactivity in the pathophysiology of catatonia.

ECT has also been established as being highly effective for catatonia\cite{2} and is suggested in benzodiazepine resistant cases and in cases with life-threatening features.\cite{1} ECT has broad effects on the central nervous system including increasing serum GABA levels and GABA_{B} activity.\cite{7,8} This lends further support to a GABA deficit model of catatonia.

In the case of clozapine, it is well-established to have superior efficacy than other antipsychotics in treatment-resistant schizophrenia. Recognized withdrawal symptoms include rebound psychosis and rebound movement disorders including dystonia and dyskinesia. Another key finding about clozapine being the only antipsychotic reported to have caused withdrawal catatonia within a 2-week period following discontinuation, as previously reported by the authors.\cite{9,10} However, it’s effect on catatonia is not fully known. Knowing that benzodiazepines and clozapine are both treatments for catatonia, it is possible that these cases are indicative of a phenomenon of “rebound” catatonia occurring when discontinuing medications used to treat catatonia. This would be analogous to the clinical presentations seen following the discontinuation of benzodiazepines (rebound anxiety) and antipsychotics (rebound psychosis).

Neuroleptic-induced catatonia is thought to be due to the blockade of D2 dopamine receptors by antipsychotics creating a hypodopaminergic state. A catatonic state could hypothetically occur on withdrawal of an agent that increases dopaminergic transmission if compensatory downregulation of dopamine receptors occurred. With clozapine increasing GABA levels in
certain areas of the brain, GABA receptor downregulation occurring after long-term clozapine use is a theoretical possibility. If receptor downregulation occurs and clozapine is then discontinued, a state of GABA hypoactivity resulting in a catatonic episode may occur.

Clozapine increases GABA levels through effects on different receptors located on GABA interneurons and through acting as an agonist at GABA B receptors. Studies on rats have found that clozapine increased levels of GABA in the hippocampus and ventral tegmental area, had minimal effects on GABA levels in the medial prefrontal cortex, and decreased GABA levels in areas of the striatum. This finding was region specific with the most significant decrease being observed in the ventral tegmental area, but was also observed in the dorsal hippocampus, nucleus accumbens, and globus pallidus.

The most striking difference between benzodiazepine and clozapine withdrawal catatonia was the response to treatment. In contrast to the 100% rate of response to benzodiazepines in the cases of benzodiazepine withdrawal catatonia, clozapine withdrawal catatonia showed a poor response to benzodiazepines. This is likely because clozapine’s primary action on the GABA system is not at the GABA receptor level where benzodiazepines exert their effect, but rather through clozapine’s effects on various receptors located on GABA interneurons.

Another mechanism in which clozapine has been shown to increase dopamine levels is through its effects on serotonin receptors. Clozapine’s antagonism of 5-HT2A receptors and activation of 5-HT1A receptors have been found to enhance dopamine release in the prefrontal cortex. The potential that clozapine may increase prefrontal cortex dopamine levels may explain its anti catatonic potential.

Withdrawal catatonia versus illness relapse: An argument could be made that the occurrence of catatonia following clozapine discontinuation within 14 days could be related to a relapse of the underlying illness rather than withdrawal effects from the medication. There are a number of reasons however that we believe the catatonia in these cases to be related to withdrawal rather than illness relapse. First, the cases of withdrawal catatonia that we identified, occurred within 14 days of clozapine discontinuation. This time frame supports a mechanism related to discontinuation as it matches the time frame in which somatic discontinuation symptoms are seen upon stopping clozapine.
Treatment modalities that are recommended for withdrawal catatonia is use of lorazepam as the medication of choice. The use of antipsychotic medications with high D2 receptor antagonism like haloperidol, should be avoided. In case of lorazepam being ineffective or a patient developing fever or not accepting oral food then ECT should be considered. General nursing care like monitoring of vital signs and ensuring adequate hydration are mandatory. One shall also use railings to avoid any fall from the bed due to the use of benzodiazepines. As there is limited data available regarding treatment of clozapine withdrawal catatonia these suggestions are based on the review of available literature. As per the observations made by us in the above two cases the first-line treatment for clozapine withdrawal catatonia is early recognition and reinstitution of clozapine. Clinical guidelines recommend that when more than 2 days of clozapine treatment have been missed, clozapine should be re-started at a dose of 12.5–25 mg and increased slowly by 25–50 mg daily over 1–2 weeks until a therapeutic dose is reached. This slow titration is to minimize the occurrence of adverse effects including orthostatic hypotension and seizures. In addition to reinstitution of clozapine, the use of adjunct benzodiazepines can be considered, but are unlikely to be effective if used as a monotherapy.

**CONCLUSION**

Clozapine is an atypical antipsychotic medication with its unique receptors binding potential and is of great interest due to its efficacy in treatment-resistant schizophrenia. This quality of clozapine being more efficacious than other antipsychotics is yet to be understood fully. There are a number of side effects too which are associated with the use of clozapine. In both of the cases described here the patient's relapse was due to an abrupt discontinuation of clozapine treatment. Clozapine may be a GABA agonist and sudden clozapine withdrawal may lead to sudden decrease in GABA activity that may contribute to the development of catatonic symptoms in vulnerable patients.[1] Our finding was that in both of these cases clozapine has caused withdrawal catatonia within 14 days of discontinuation. The treatment for catatonia secondary to sudden clozapine withdrawal is use of benzodiazepines and /or restarting clozapine and ECTs if required.

Clinicians should be attentive towards the emergence of catatonia symptoms on abrupt withdrawal of clozapine and inform their patients and relatives that missing the regular dose of the medication for 1 or 2 days may cause unpleasant and severe withdrawal symptoms.

**CONFLICT OF INTEREST: NIL**
REFERENCES


