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CASE REPORT

Clozapine for Persistent Manic Agitation Following Haloperidol-Associated Neuroleptic Malignant Syndrome: A Case Report

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ABSTRACT

A 35-year-old man with bipolar affective disorder presented during a manic episode and was treated with intramuscular haloperidol 20 mg/day and promethazine 100 mg/day in divided doses, along with lithium 800 mg/day. On the fourth day of treatment, he developed high-grade fever, generalized rigidity, tremors, mutism, echolalia, altered consciousness, and marked autonomic instability, including tachycardia and labile blood pressure. Serum creatine phosphokinase was 2800 U/L, with leukocytosis and elevated CK-MB; troponin I was normal. A diagnosis of Neuroleptic malignant syndrome (NMS) was made, and all psychotropic medications were discontinued. He was treated with intravenous fluids, external cooling, and bromocriptine 15 mg/day. The fever, rigidity, and autonomic abnormalities improved over approximately 72 hours. However, after resolution of the acute NMS manifestations, severe agitation, aggression, and insomnia persisted. Lorazepam and nitrazepam provided inadequate behavioural control, while electroconvulsive therapy was considered unsuitable because of ongoing autonomic instability. Clozapine was initiated at 25 mg/day with close clinical and laboratory monitoring. Within 48 hours, marked reduction in agitation was observed, followed by improved cooperation and sleep. By the fifth day, behavioural stabilization was evident, without recurrence of fever, rigidity, autonomic instability, or clinically significant CPK elevation. This case illustrates the therapeutic challenge of persistent manic agitation following NMS. Clozapine may be considered in carefully selected patients when conventional antipsychotic treatment is considered unsuitable and other interventions are ineffective or temporarily contraindicated. However, clozapine itself can cause NMS Its use following NMS should therefore involve complete clinical resolution of the acute syndrome, conservative dosing, and close monitoring.

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KEYWORDS

• Neuroleptic malignant syndrome • Clozapine • mania • Bipolar disorder • Antipsychotic rechallenge • Agitation • Aggression • Treatment-resistant mania

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal adverse reaction associated primarily with dopamine receptor antagonists and, less commonly, with abrupt withdrawal of dopaminergic medications. The syndrome is characterized by a constellation of hyperthermia, muscular rigidity, altered mental status, and autonomic dysfunction, accompanied frequently by elevations in creatine phosphokinase (CPK) and other biochemical markers of muscle injury.[1,2] Several factors increase the risk of NMS, including exposure to high-potency antipsychotics, high doses or rapid dose escalation, parenteral administration, severe psychomotor agitation, dehydration, and concomitant use of medications such as lithium.[1,3] Management primarily involves immediate discontinuation of the offending medication, intensive supportive treatment, correction of fluid and electrolyte abnormalities, temperature control, and, in selected patients, pharmacological interventions such as bromocriptine or dantrolene.[1,3] An additional therapeutic challenge arises when the underlying psychiatric disorder remains active after the acute manifestations of NMS have resolved. This is particularly relevant in patients with severe mania. Although benzodiazepines may be useful, they may not adequately control severe manic symptoms. Electroconvulsive therapy (ECT) can be an effective treatment for severe mania but may be temporarily unsuitable when significant medical or cardiovascular instability persists. Reintroduction of antipsychotic medication requires careful consideration because of the potential risk of recurrent NMS. Clozapine presents a potentially useful but complex option in such circumstances. Although clozapine itself has been associated with NMS, published evidence suggests that it has been successfully used following NMS caused by other antipsychotics in selected patients.[5,6] Clozapine also has evidence supporting its use in severe treatment-resistant bipolar disorder and in patients with prominent aggression.[7] Nevertheless, the available evidence concerning clozapine following NMS is derived largely from case reports and case series.

CASE REPORT

A 35-year-old man with a diagnosis of bipolar affective disorder was admitted during his second manic episode. At admission, he exhibited prominent manic symptoms, including elevated and irritable mood, grandiose ideas, markedly reduced sleep, increased psychomotor activity, irritability, and severe uncontrollable aggression. There was no history of neuroleptic malignant syndrome or other serious adverse reaction to psychotropic medication. Because of the severity of his behavioural disturbance, intramuscular haloperidol 20 mg/day and intramuscular promethazine 100 mg/day were administered in divided doses. Lithium was prescribed at a total dose of 800 mg/day in divided doses. On the fourth day following initiation of treatment, the patient developed an acute febrile illness accompanied by severe generalized muscular rigidity, tremors, agitation, mutism, echolalia, altered consciousness, and marked autonomic instability. His temperature was 102°F. He developed tachycardia and marked fluctuations in blood pressure, with systolic blood pressure ranging between 180 and 210 mmHg. Laboratory investigations demonstrated a CPK level of 2800 U/L and leukocytosis. CK-MB was elevated at 71 U/L, whereas troponin I was within normal limits. Serum electrolyte analysis showed sodium 146 mmol/L, potassium 3.3 mmol/L, and chloride 111 mmol/L. Gamma-glutamyl transferase was within normal limits, and urine myoglobin was negative. Electrocardiography demonstrated sinus tachycardia. The overall clinical presentation, recent exposure to high-potency intramuscular haloperidol, muscular rigidity, hyperthermia, altered consciousness, autonomic instability, and elevated CPK were consistent with NMS. The diagnosis was made according to Levenson's criteria.[4] All

psychotropic medications were discontinued. The patient was managed with intravenous fluids and external cooling measures. Bromocriptine was initiated at a total daily dose of 15 mg in divided doses. Close monitoring of vital signs, neurological status, and biochemical parameters was undertaken.

Over the next 72 hours, the patient's fever, muscular rigidity, and autonomic abnormalities improved substantially. His clinical state subsequently became medically more stable. However, after resolution of the acute manifestations of NMS, the patient remained severely agitated, aggressive, and unable to sleep. Lorazepam 4 mg/day and nitrazepam 10 mg/day were administered; however, clinically significant agitation and insomnia persisted. ECT was considered because of the severity of the manic state but was deferred because of persistent autonomic instability. Given the severity of the persistent manic and aggressive symptoms and the limited therapeutic alternatives, cautious reintroduction of an antipsychotic was considered. After clinical resolution of the acute NMS manifestations, clozapine was initiated at a low dose of 25 mg/day. The patient was monitored closely for recurrence of hyperthermia, muscular rigidity, autonomic instability, altered consciousness, and biochemical evidence of muscle injury. Haematological monitoring and electrocardiographic monitoring were also performed. A marked reduction in agitation was observed within approximately 48 hours of clozapine initiation (Figure 1). By the third day, the patient demonstrated improved cooperation and was able to initiate sleep. Continued behavioural stabilization was observed by the fifth day. There was no clinical recurrence of fever, muscular rigidity, autonomic instability, or other characteristic features of NMS during the observed period. No clinically significant secondary elevation of CPK was reported. The patient was subsequently discharged in a clinically stable condition on clozapine monotherapy. During monthly follow up for 3 months he maintained the improvement.

DISCUSSION

The present case demonstrates the considerable therapeutic difficulty encountered when severe mania persists following resolution of NMS. The patient developed a classical clinical picture of NMS shortly after receiving high-dose intramuscular haloperidol in the context of severe psychomotor agitation and concomitant lithium treatment.

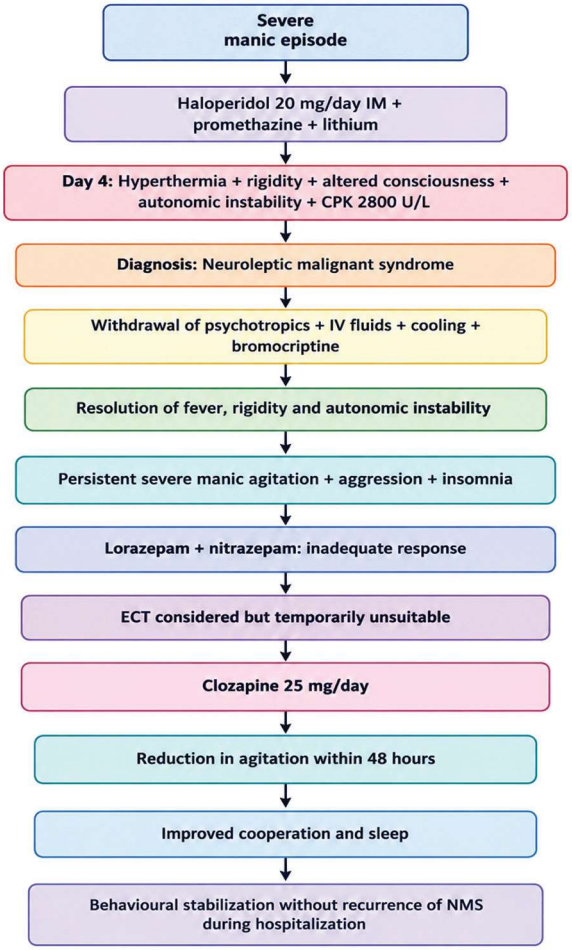


Figure 1: Clinical timeline

The presence of hyperthermia, generalized rigidity, altered consciousness, autonomic instability, leukocytosis, and a markedly elevated CPK level strongly supported the diagnosis. NMS remains a clinical diagnosis, and Levenson's criteria provide a useful framework incorporating major features such as fever and rigidity with minor features including tachycardia, abnormal blood pressure, tachypnoea, altered consciousness, diaphoresis, leukocytosis, and laboratory evidence of muscle injury.[4] In this patient, multiple major and minor features were present in close temporal association with high-potency antipsychotic exposure. The patient's CK-MB was elevated despite a normal troponin I and an ECG showing sinus tachycardia. In the context of generalized skeletal muscle

injury and elevated total CPK, an isolated CK-MB elevation may occur without myocardial injury. The normal troponin and absence of ECG evidence of acute myocardial ischemia supported a non-cardiac explanation for the CK-MB elevation in this case. Several factors may have contributed to the development of NMS. The patient was receiving a relatively high dose of intramuscular haloperidol in the setting of severe psychomotor agitation. Parenteral administration and high-potency dopamine antagonism have been recognized risk factors for NMS.[1,3] Concomitant lithium treatment may also increase susceptibility in some clinical circumstances. The combination of severe agitation, high-dose parenteral haloperidol, and lithium therefore represented a clinically important risk context.

The initial management was based on immediate withdrawal of psychotropic medication, intravenous fluid replacement, external cooling, and bromocriptine. The patient's fever, rigidity, and autonomic abnormalities improved over approximately 72 hours, suggesting adequate resolution of the acute syndrome. However, the persistence of severe behavioural disturbance after resolution of the classical manifestations of NMS created a second clinical challenge. An important consideration in such cases is whether continuing agitation represents incomplete resolution of NMS, delirium, medication withdrawal, or persistence of the underlying psychiatric disorder. Residual NMS may include weakness, fatigue, cognitive disturbance, and other nonspecific symptoms. Conversely, severe mania may continue to manifest with reduced need for sleep, increased psychomotor activity, irritability, grandiosity, aggression, and behavioural disorganization even after the physical manifestations of NMS have resolved. In the present case, the persistence of marked agitation and insomnia despite resolution of fever, rigidity, and autonomic instability was considered more consistent with persistence of the manic episode (Table 1). This distinction was important because treatment aimed at NMS would not adequately address the underlying manic syndrome, whereas untreated severe mania posed continuing risks to the patient and caregivers.

Table 1: Clinical differentiation of persistent agitation after NMS

Clinical feature	Residual/ ongoing NMS	Delirium	Persistent mania	Present case after NMS resolution
Hyperthermia	May persist	May occur	Usually absent	Resolved
Generalized rigidity	May persist	Variable	Absent	Resolved
Autonomic instability	May persist	May occur	Usually absent	Improved/resolved
Altered consciousness	May occur	Characteristic	Usually absent	Improved
Reduced need for sleep	Nonspecific	Sleep-wake disruption	Characteristic	Present
Increased psychomotor activity	May occur	Variable	Characteristic	Present
Grandiosity	Not characteristic	Not characteristic	Characteristic	Present initially
Aggression	May occur	May occur	Common in severe mania	Persistent
CPK elevation	Common	Usually absent	Usually absent	Declining/resolved
Response to clozapine	Not diagnostic	Not diagnostic	May improve	Marked improvement

Reintroduction of antipsychotic medication following NMS is a clinically difficult decision. Antipsychotics remain among the most effective treatments for severe mania, but clinicians may understandably be reluctant to re-expose a patient to dopamine antagonists after a potentially life-threatening adverse reaction. Benzodiazepines may be useful in managing agitation associated with mania and NMS, but their efficacy may be inadequate in severe persistent mania. In the present case, lorazepam and nitrazepam did not provide sufficient behavioural control. ECT was considered but was temporarily unsuitable because of ongoing autonomic instability. These circumstances left the treating team with

limited options. Clozapine was selected after the acute NMS syndrome had resolved because of its established clinical utility in severe psychotic and behavioural disorders and its potential role in treatment-resistant bipolar disorder. A systematic review found evidence supporting clozapine in treatment-resistant bipolar disorder, including improvements in manic, depressive, psychotic, and aggressive symptoms.[7] Although the evidence base is considerably smaller than that for standard antimanic treatments, clozapine may have particular clinical utility when severe aggression and behavioural dyscontrol are prominent.

The decision to use clozapine following NMS requires particular caution because clozapine itself can produce NMS.[5] Nevertheless, there is evidence that clozapine can sometimes be used successfully following NMS associated with another antipsychotic. A systematic review of clozapine rechallenge following NMS identified 67 published cases. Among 38 patients who underwent clozapine rechallenge following NMS associated with a non-clozapine antipsychotic, 30 cases (79%) were reported as successful, with no reported mortality.[6] The present case is consistent with this literature. Clozapine was introduced only after the acute manifestations of NMS had clinically resolved and at a conservative dose of 25 mg/day. The patient demonstrated rapid improvement in agitation and sleep without clinical recurrence of NMS during the observed hospitalization.

Clinical implications

This case has implications for the management of severe mania following NMS. The occurrence of NMS does not necessarily imply that all future antipsychotic treatment must be permanently avoided. However, any decision to restart antipsychotic therapy requires a careful assessment of risks and benefits.

CONCLUSION

The present case suggests that clozapine may be considered as a carefully monitored treatment option in selected patients with persistent severe mania following NMS when alternative interventions are ineffective, unavailable, or temporarily unsuitable.

Conflict of interests: None

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