Suspected Neuroleptic Malignant Syndrome During Quetiapine-Clozapine Cross-Titration

Steven C. Stoner, PharmD, BCPP, and Amy Berry, PharmD Candidate

Neuroleptic malignant syndrome (NMS) is a physiologic phenomenon that has been associated with the use of both first- and second-generation antipsychotics resultant to their ability to block dopamine blockade in the basal ganglia and hypothalamic regions of the brain. The typical reaction involves the presentation of muscle rigidity, changes in mental status, temperature elevation, labile blood pressure, and elevations in creatinine kinase and white blood cell counts. The reaction is most often reported early in the course of therapy but is well documented to have the potential to occur at any point in time. Untreated NMS can be fatal, often from secondary causes such as deep venous thrombosis and pulmonary embolism. Treatment involves immediate discontinuation of the offending agent, supportive therapy of clinical symptoms, and may include the use of the skeletal muscle relaxant, dantrolene sodium, or the dopaminergic agents bromocriptine or amantadine. In this case, we present a patient who developed symptoms of NMS during the cross-taper and conversion from quetiapine to clozapine. The patient was treated for NMS; however, his clinical diagnosis was never able to be definitively determined as he was initially evaluated for septicemia and later treated for suspected bacterial infection with antibiotics, and clozapine-associated side effects cannot be ruled-out as a contributing source to the clinical presentation. The estimated Naranjo Scale score for this case report is 3.

Keywords: quetiapine; clozapine; neuroleptic malignant syndrome; NMS

Neuroleptic malignant syndrome (NMS) is a serious and sometimes fatal syndrome most often associated with treatment with antipsychotic and some antiemetic medications. The classical presentation of NMS includes autonomic and neurological signs and symptoms such as muscle rigidity, hyperthermia, hypertension, diaphoresis, and catatonia. First-generation antipsychotics (ie, haloperidol, fluphenazine, chlorpromazine) are some of the common medications that have been associated with NMS; however, NMS has also been reported with second-generation antipsychotic agents such as risperidone, olanzapine, clozapine, quetiapine, ziprasidone, and aripiprazole.1-13 The risk of developing NMS is considered greatest in the first 2 weeks after initiating therapy and has also been associated with rapid dose escalation.14,15 Early recognition, diagnosis, and treatment are keys in preventing NMS-related death. One barrier to early intervention is the similarity of NMS signs and symptoms to signs and symptoms of other diseases, including heat stroke, lethal catatonia (LC), malignant hyperthermia (MH), serotonin syndrome, dehydration, infection, and alcohol withdrawal. These similarities make it imperative to conduct a critical assessment and evaluation. Another potential difficulty in recognizing NMS with second-generation...
antipsychotics is their apparent association with lower overall incidence of rigidity and fever, though still present in the majority of reported cases.16

Classic early NMS neurological symptoms include extrapyramidal symptoms (EPS), which have been shown to progress to “lead-pipe” muscle rigidity.15 Other symptoms commonly reported include mental status changes (confusion), hyperthermia (temperature between 38°C and 40°C [100.4°F-104°F]), diaphoresis, catatonia, signs of autonomic dysfunction (ie, hypertension, tachycardia, and urinary incontinence), and abnormal laboratory measures of elevated creatinine phosphokinase (CPK) and leukocytes.14,15,17-19 With the differential diagnosis being complicated, the establishment of timeline associations with medication and onset of clinical symptom presentation is of importance. There are several key differentiating features for NMS from other disorders. Diaphoresis typically does not occur with dehydration or heat stroke. Additionally, unlike NMS, MH is most common in patients who have received inhaled anesthetics, whereas LC is most commonly associated in patient with organic brain or other functional illnesses.14,15,18,20 Infection and alcohol withdrawal are not usually associated with the early presentation of “lead-pipe” muscle rigidity, but may instead present with muscle spasms or tremors.

Treatment of NMS is largely supportive and mortality rates increase significantly when early intervention is delayed. The offending medication should be stopped immediately and fluid and electrolyte imbalances should be restored.17 Additionally, the basal temperature should be reduced by removing covers and clothing, applying cool washcloths, and using antipyretic agents. Cardiac, respiratory, and renal complications can occur and should be monitored.15,17 Additional supportive measures to prevent the development of deep vein thrombosis (DVT), pulmonary embolism, and decubitus ulcers may be necessary as these may contribute to increased mortality.14,18 The chances of achieving a favorable outcome are also improved if adequate oxygenation can be maintained along with frequent monitoring of vital signs and assuring proper hydration and urine output.18

Some of the pharmacologic agents that have been shown to reduce the severity of symptoms of NMS include the dopaminergic agents, amantadine and bromocriptine, or the skeletal muscle relaxant, dantrolene sodium.14,17-19 Once properly identified and treated, NMS typically resolves over a course of 7 to 10 days. Rechallenging patients who have experienced NMS with antipsychotics is not an absolute contraindication, though most data support waiting at least 5 days and up to 2 weeks before reintroduction of the suspected offending agent.17,21,22

In the following case report, we present the clinical scenario where symptoms consistent with NMS developed while in the process of converting from quetiapine to clozapine. The patient was later successfully rechallenged with a different second-generation antipsychotic.

**Case Report**

At the time of the suspected NMS-related adverse event, a 49-year-old Caucasian male was being treated for a delusional disorder and depression in a long-term care psychiatric facility. The patient’s symptoms of mental illness began approximately 10 years prior; however, he was not aggressively treated until approximately 2 years prior to the suspected NMS event that we describe. The patient’s medical diagnoses included hypothyroidism, chronic constipation, and type II diabetes, which was controlled with diet at the time of the suspected NMS event. When the patient was admitted to the long-term care facility, he was treated for symptoms of depression and psychosis (delusional and paranoid) with the combination of mirtazapine 30 mg at bedtime and quetiapine 300 mg twice daily (prior treatment with risperidone and loxapine failed). The patient was also taking levothyroxine 0.1 mg daily as thyroid supplementation. The patient had been on quetiapine for approximately 4 months, and despite the use of a dose that some clinicians may consider suboptimal dosing, it was considered a treatment failure. Given the patient’s history of poor response to both first- and second-generation antipsychotics, he was initiated on clozapine with plans to titrate up on clozapine and taper off of quetiapine concurrently. Quetiapine was reduced daily in 50 mg increments, whereas clozapine was initiated at 12.5 mg once daily for 1 day, then increased to 25 mg daily for 1 day, and then increased by 25 mg daily thereafter. After 12 days of being on the combination quetiapine, clozapine, divalproex sodium, and mirtazapine, the patient began to develop symptoms consistent with NMS. The patient was transferred to a local hospital’s emergency department where he was
evaluated, admitted, and treated for the differential diagnosis of NMS and septicemia.

The clinical course (see Table 1) of developing NMS-like symptoms occurred 12 days into the cross-titration while on doses of 50 mg of quetiapine at bedtime and 150 mg twice daily of clozapine. The patient was also on mirtazapine 30 mg at bedtime, divalproex sodium 1500 mg twice daily, and levothyroxine 0.1 mg once daily. On the morning of the NMS-like event, the patient had complained of low back pain in the early morning hours though he refused any treatment. Additionally, as the day progressed there were significant changes in cognition as the patient became incoherent, difficult to arouse, and refused to eat, he exhibited a total body tremor with abnormal abrupt myokymic movements of his limbs, and displayed extreme disturbances in gait with ataxia and subsequent falls. The patient’s blood pressure showed signs of fluctuation with orthostatic hypotension and mild tachycardia (range of 132/80 to 80/50 with rates ranging from 64 to 131) in the 48 hours prior to being transferred. On the day of the medical transfer, the patient was afebrile until the late evening when he recorded a temperature of 102.6°F, and he was administered 975 mg of acetaminophen. After 30 minutes, the patient’s temperature had continued to increase and was found to be 104.5°F, which resulted in the patient being sent to the medical emergency department with subsequent medical admission.

During the medical hospitalization, initial treatment interventions included the discontinuation of all psychotropic medications, the administration of a single dose of dantrolene sodium 25 mg, and the initiation of bromocriptine 2.5 mg twice daily. Because infection was a suspected source of fever, intravenous ceftriaxone (1 g per 24 hours) was administered prior to the confirmation of infection by culture and sensitivity. Hematology, serum chemistry, and blood and urine cultures were obtained in addition to chest X-rays, lumbar puncture, and computed tomographies (CTs) of the chest, head, and abdomen. Admitting lab values showed a white blood cell (WBC) count of 7.2 K/MM³ (4.0-10.8 K/MM³), absolute neutrophil count of 5256 cells/μL, red blood cell count of 4.54 M/MM³ (4.60-6.20 M/MM³), a hemoglobin of 13.2 g/dL (13.0-17.0 g/dL), a hematocrit of 38.4% (40.0%-50.0%), a valproic acid level of 99 mg/L (50-120 mg/L), and an aspartate aminotransferase (AST) of 13 IU/L (<35 IU/L). Throughout the course of the medical hospitalization, the WBC count ranged from 4.8 to 6.7 K/MM³ (4.0-10.8 K/MM³). Midstream urine collection was negative for nitrites and leukocytes, and a creatinine kinase (CK) was 65 IU/L (21-232 IU/L). The CK ranged between 76 and 93 IU/L (21-232 IU/L) during the course of hospitalization. Because it was felt that the clinical

<table>
<thead>
<tr>
<th>Time</th>
<th>Medications</th>
<th>Presentation</th>
</tr>
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<tbody>
<tr>
<td>Day –12</td>
<td>Quetiapine 600 mg bid; clozapine 12 mg hs; mirtazapine 30 mg hs; divalproex 1500 mg bid; levothyroxine 0.1 mg daily</td>
<td>Paranoid, delusional, irritable</td>
</tr>
<tr>
<td>Day 0</td>
<td>Quetiapine 50 mg hs; clozapine 150 mg bid; mirtazapine 30 mg hs; divalproex 1500 mg bid; levothyroxine 0.1 mg daily</td>
<td>Low back pain, lethargic, incoherent speech, body tremor, myokymic movements, orthostatic, mild tachycardia, elevated temperature</td>
</tr>
<tr>
<td>Day 0 (post-transfer)</td>
<td>Psychotropics discontinued; dantrolene and bromocriptine initiated; ceftriaxone and doxycycline initiated</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>Doxycycline discontinued; ceftriaxone increased to 2 g</td>
<td>Fever resolved, CSF negative, blood cultures negative, CT head negative, chest X-ray shows possible infiltrate and pulmonary interstitial edema</td>
</tr>
<tr>
<td>Days 3-5</td>
<td></td>
<td>Stable, returned to psychiatric treatment facility</td>
</tr>
<tr>
<td>Day 8</td>
<td>Bromocriptine 2.5 mg bid; levofloxacin 500 mg daily; metoprolol 25 mg daily; glyburide 2.5 mg daily; ferrous sulfate 324 mg daily; docusate calcium 240 mg daily; levothyroxine 0.1 mg daily</td>
<td></td>
</tr>
<tr>
<td>Day 30</td>
<td>Started on risperidone 0.5 mg bid</td>
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*Day 0 = day of NMS symptom presentation.*
presentation was most likely NMS, the antibiotic was also discontinued. Following the discontinuation of ceftriaxone, the patient again became febrile within 24 hours and was empirically started on ceftriaxone 1 g intravenously and doxycycline 100 mg twice daily with the patient again becoming afebrile after antibiotic reinitiation. Doxycycline was discontinued within 24 hours and ceftriaxone was increased to 2 g intravenously every 24 hours.

Despite the use of antibiotics, the patient’s blood cultures obtained prior to the initiation of antibiotics showed no growth of bacteria after 5 days, the CSF showed no growth after 3 days, the CSF gram stain was negative, urine cultures were negative, and a test of the cerebrospinal fluid (CSF) for antigens was negative. The chest X ray on the day of medical transfer was normal though follow-up X rays showed possible bilateral interstitial infiltrates (pulmonary interstitial edema), left lung base atelectasis, and bilateral pleural effusions. Further testing showed a CT of the head to be negative, a CT of the chest showed a possible infiltrate and pleural thickening though it was noted to be possible scarring secondary to prior gunshot wound, and a CT of the abdomen showed no evidence of a mass or obstruction. The patient was released back to the inpatient psychiatric facility after 8 days. At the time of discharge from the medical hospital and return to the long-term care psychiatric hospital, the patient’s medications consisted of levofloxacin 500 mg daily (started at discharge from medical facility), metoprolol 25 mg twice daily, bromocriptine 2.5 mg twice daily, glyburide 2.5 mg daily, ferrous sulfate 324 mg daily, docusate calcium 240 mg daily, and levothyroxine 0.1 mg daily.

Following the patient’s return to psychiatric care, he continued to exhibit a low-grade fever ranging from 100.3°F to 102°F. Blood pressure readings continued to fluctuate with several noted to be below 90/60 and he displayed delayed response times to verbal stimuli, which necessitated the discontinuation of both metoprolol and bromocriptine. Levofloxacin was continued for an additional 7 days; however, at no time did workup for bacterial infectious origins prove conclusive.

Thirty days following the discontinuation of all antipsychotic medications, the patient was restarted on antipsychotic treatment in the form of risperidone 0.5 mg twice daily. The patient refused to take risperidone and was subsequently changed to loxapine and then later olanzapine. The patient was psychiatrically stabilized on olanzapine 10 mg daily and was discharged from psychiatric care 79 days following the original development of the NMS-like symptoms. The patient’s medications upon discharge were the following: olanzapine 10 mg at bedtime, clonazepam 1 mg at bedtime, gemfibrozil 600 mg twice daily, levothyroxine 0.1 mg daily, and ferrous sulfate 324 mg daily. No further NMS-like symptoms were reported.

**Discussion**

The case of suspected NMS we describe is an atypical presentation and leaves some question of diagnostic interpretation, given its unique clinical presentation (normal WBC and CPK) and treatment as both a suspected bacterial infection and NMS. There are multiple explanations for developing NMS along with several risk factors that have been identified. Antipsychotic-associated blockade of dopamine receptors in the basal ganglia and hypothalamus is thought to account for the muscle rigidity and thermal dysregulation that is seen with NMS. 

However, multiple mechanisms are thought to contribute to the overall presentation of NMS and may also include an imbalance between dopamine and gamma-aminobutyric acid (GABA)-ergic neurotransmitters, increased norepinephrine, impaired second messenger systems as well as a possible genetic predisposition. 

Patients on high doses of antipsychotic medications, those who experience rapid titration, or those that receive the antipsychotic through parenteral means appear to be at the greatest risk for developing NMS. 

Other risk factors include physical exhaustion, agitation, dehydration, presence of concurrent mood disorder, and the sudden discontinuation of anti-Parkinson medications. In this particular case we describe, the patient had a limited number of risk factors that included the use of antipsychotic medication in a manner that used 2 agents at 1 time which may be considered aggressive use of polypharmacy and potentially excessive dopamine receptor blockade; however, both titration schedules by themselves would not be considered aggressive.

Initiating an appropriate antipsychotic rechallenge after experiencing NMS is another clinical dilemma. A review of 41 cases of antipsychotic rechallenge following the development of NMS looked at the outcome following rechallenge with a
structurally similar or dissimilar antipsychotic. The findings suggested the recurrence of NMS is unrelated to the type of antipsychotic being rechallenged with; however, there was an apparent relationship between the amount of time allowed between the NMS episode and rechallenge, suggesting a 5-day period before rechallenge reduces the recurrence of NMS. Other evidence suggests that antipsychotic rechallenge <2 weeks after an NMS episode carries a risk of NMS recurrence. In the case that we report, 30 days elapsed before rechallenge with an antipsychotic.

The patient we report on exhibited symptoms of an elevated basal temperature measuring >38°C, a significant change in mental status, impaired coordination, and autonomic dysfunction. Unfortunately, these symptoms are consistent with both the NMS and bacterial infection diagnoses that the patient was treated for. During the patient's initial presentation, he was discontinued off of clozapine, quetiapine, divalproe sodium, and mirtazapine. Dantrolene sodium, bromocriptine, doxycycline, and ceftriaxone were initiated while the patient was evaluated for NMS and septicemia and later treated for suspected bacterial infection. Confounding the clinical presentation and the subsequent resolution of NMS-like symptoms was the later use of a second antibiotic, levofloxacin, which was initiated at 500 mg once daily and was continued for 7 days following the patient's return to the psychiatric treatment facility.

There are some notable observations from this patient's case. Blood and urine were negative for bacteria, and initial and follow-up chest X rays were negative for infiltrate. The timing of the possible NMS event coincides with the combined titration of clozapine and tapering of quetiapine, suggesting that this rate of conversion may have contributed to the suspected NMS presentation. In addition, NMS typically resolves in 7 to 10 days after discontinuation of the antipsychotic, which is consistent with the time-frame observed for this patient's hospitalization.

Another consideration that should be mentioned is the possibility that the patient's clinical presentation was neither NMS nor septicemia. The orthostatic hypotensive episodes, increased heart rate, and excessive sedation may be explained by the use of quetiapine, clozapine, divalproe sodium, and mirtazapine and their pharmacodynamic properties acting on α, β, and histamine receptors, though the symptoms we describe were extreme. Additionally, the development of idiosyncratic fevers (100.4°F to 104°F) that spontaneously resolve have been reported to occur and resolve during the initial 3 weeks of clozapine therapy.

The estimated Naranjo Scale score for this case report was 3. This score indicates that the adverse reaction we describe is “possible.” The score of 3 was determined based on the documentation of conclusive reports for both first- and second-generation antipsychotics, the event we described occurred after a new antipsychotic medication was given, there was medical improvement when drug was discontinued, and the reaction was more severe during the cross-titration of 2 antipsychotic medications.

**Conclusion**

The difficulty of differential diagnosis often leads to misdiagnosis of NMS early in its presentation. Clinicians need to be aware of the patient's risk of NMS when considering both first- and second-generation antipsychotic as well as some antiemetic medications. Although first-generation antipsychotics have a higher reported rate of NMS than second-generation antipsychotics, there is an NMS risk for both classes of medication. Early diagnosis of NMS, along with supportive care, and discontinuation of the offending medication are pivotal in favorable outcomes for patients that develop NMS. There are several postulates as to the etiology of NMS; however, no single theory seems to explain all the neurological and autonomic signs of NMS. The following have been offered as possible causes of NMS: blockage of dopamine in the basal ganglia and hypothalamus causing difficulty in heat dissipation, an imbalance between dopamine and GABA-ergic neurotransmitters, and involvement of the frontal lobe with secondary involvement of the EPS of the brain. Pharmacologic treatments with dopamine agonists, such as bromocriptine and amantadine, aid in rapid reversal of the dopamine blockade. Agents such as diazepam are GABA-ergic, which helps decrease muscle rigidity and corrects any imbalance between dopamine and GABA-ergic neurotransmitters. Risk of NMS upon rechallenge does not appear to be related to the antipsychotic itself, rather the amount of time allowed between the NMS episode and reinitiating the antipsychotic.
Further research is needed concerning the mechanism that causes NMS. Research on NMS will create better treatment and prevention protocols for this potentially lethal syndrome. Understanding the underlying causes of NMS will also give greater understanding of the autonomic and neurological functioning of the human body that are undermined by antipsychotics in patients that suffer from NMS. Understanding NMS will also help identify patients that are predisposed to developing NMS, so that more appropriate treatment therapies can be used for those patients. Averting NMS will avoid costly emergency and general hospital care expenses. Diagnosis of NMS has increased considerably since it was first identified. Clinicians must be vigilant in diagnosis and reporting NMS. Diagnosis and reporting of NMS will guide further research and yield better outcomes for patients that have developed NMS or will develop NMS.

In summary, this case represents an example of a patient who developed suspected NMS while being treated with the combination of second-generation antipsychotics quetiapine and clozapine. This illustrates the importance of continuing to be diligent in monitoring a patient's response and tolerability regardless of the types or how long the antipsychotic medication has been used. This particular case also represents a situation in which rechallenge with an alternative second-generation antipsychotic was successfully implemented.

References