

# Benzodiazepines for Treatment of Neuroleptic Malignant Syndrome

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**N**euroleptic malignant syndrome (NMS)—a rare, acute disorder of thermoregulation and neuromotor control—is an idiosyncratic response to dopamine receptor blockade. The term *hypodopaminergic, hyperpyrexia syndrome* may more accurately describe NMS. The mortality rate for untreated NMS is approximately 21%. Although treatment of NMS generally has been supportive, use of pharmacologic therapy has been explored in recent years.

This article discusses the clinical presentation, pathogenesis, and risk factors for developing NMS, including the similarities between NMS and cocaine-induced rhabdomyolysis. The pharmacologic treatment of the syndrome is discussed, with an emphasis on the use of benzodiazepines. Two cases are presented in which lorazepam was used successfully for treatment.

## NEUROLEPTIC MALIGNANT SYNDROME

### Clinical Presentation

NMS is characterized by generalized muscle rigidity, rhabdomyolysis, myoglobinuria, fever, altered mental status, tremor, and autonomic instability.<sup>1</sup>

Creatine kinase (CK) levels always are increased in NMS and can range from 2000 to 15,000 U/L; in rare cases, CK levels may exceed 100,000 U/L.<sup>1</sup> An elevated CK level is highly sensitive for NMS; therefore, the absence of this finding rules against the diagnosis of NMS. An increased CK level is a nonspecific sign, however, as it may be markedly increased with agitation, strenuous physical exercise, dystonia, and/or intramuscular injection.

Leukocyte counts usually are increased to 15,000 to 30,000 × 10<sup>3</sup>/mm<sup>3</sup> in NMS, with a shift to the left occurring in approximately 40% of cases.<sup>1</sup> In addition, serum levels of alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase usually are elevated and indicate liver involvement.

### Pathophysiology

As indicated by the name, NMS is associated with administration of neuroleptic medications. The exact mechanism of NMS remains unclear, but dopamine

deficiency and/or dopamine blockade are hypothesized in the pathogenesis of NMS. Reduced dopamine activity in various areas of the brain (ie, hypothalamus, nigrostriatal system, corticolimbic tracts) may serve to explain the clinical features of NMS. Dopamine reduction in the hypothalamus may cause fever and autonomic instability; in the nigrostriatal system, dopamine reduction may lead to rigidity; and a reduction in corticolimbic dopamine activity may explain the altered consciousness.<sup>2</sup> The dopamine blocking theory does not, however, explain why NMS may develop in a given patient, and additional genetic (ie, a predisposition similar to that seen in malignant hyperthermia),<sup>2</sup> constitutional, environmental, and pharmacological factors likely interact to produce the syndrome.

NMS has been reported in 0.2% to 1.9% of patients taking neuroleptic agents. Several factors likely account for this large variability in frequency, including differences in study methods and diagnostic criteria for NMS.<sup>2</sup> NMS has been associated most frequently with high-potency agents (eg, haloperidol), although it also has been associated with low-potency neuroleptic drugs (eg, chlorpromazine). In addition, NMS occurs with dopamine receptor blocking agents used for other purposes, such as phenothiazine antiemetics (eg, prochlorperazine), antipsychotics as adjuncts to anesthesia (eg, droperidol), and amoxapine (an antidepressant with a neuroleptic-like metabolite).

NMS can occur when antiparkinsonian agents (eg, amantadine, carbidopa-levodopa) are decreased or discontinued. Dopamine-depleting agents (eg, reserpine, tetrabenazine) also may cause NMS. Several reports of NMS have been ascribed to atypical antipsychotics, including clozapine and risperidone. Drugs associated with NMS are listed in **Table 1**.

Cocaine has been reported to produce rhabdomyolysis and myoglobinuria in some studies.<sup>3-7</sup> The resemblance of these cases to the clinical picture of

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**Table 1.** Drugs Associated with Neuroleptic Malignant Syndrome (NMS)

Drug Class	Specific Agents
Butyrophenones	Haloperidol, bromperidol, droperidol
Phenothiazines	Fluphenazine, chlorpropamine, thioridazine, trimeprazine, levomepromazine, prochlorperazine
Thioxanthenes	Thiothixene
Dibenzoxazepines	Loxapine
Dopamine-metoclopramide	Alpha-methyltyrosine
Dopamine-depleting agents	Reserpine, tetrabenazine
Atypical antipsychotic agents	Clozapine, risperidone, olanzapine*
Withdrawal of dopamine agonist agents	Levodopa, amantidine, levodopa/carbidopa

\*These agents have been associated with NMS in case reports only.

NMS raises the question of whether cocaine-induced rhabdomyolysis is a variant of NMS.<sup>8,9</sup>

The mechanism by which cocaine may induce NMS is unknown. However, hypothalamic dopaminergic involvement may account for hyperthermia following cocaine use.<sup>10</sup> Cocaine may induce excessive dopaminergic activity by blocking the reuptake of dopamine, thereby exerting an agonist effect and depleting dopamine storage. In experimental studies,<sup>10</sup> dopamine antagonists such as haloperidol have been shown to produce hypothermia at relatively low temperatures and hyperthermia when ambient temperature exceeds 32°C. The presence of hyperthermia, depressed level of consciousness, or delirium and autonomic instability with rhabdomyolysis is suggestive of NMS. This resemblance led Kosten and Kleber<sup>11</sup> to propose a common pathogenic mechanism for cocaine-induced rhabdomyolysis and NMS.

#### Risk Factors

The ratio of males to females who develop NMS is 3:2, and the mean reported age of onset is approximately 40 years. Possible risk factors for developing NMS include presence of an organic mental disorder, agitation, dehydration, use and rate of concurrent psychotropic agents (eg, lithium), and route and dose of neuroleptic administration.

#### Clinical Course

Typically, the syndrome progresses rapidly and develops completely in 24 to 48 hours. The average duration of NMS is 7 to 14 days, but it may remain for up to 30 days. In some cases, a residual catatonic-parkinsonian state following NMS may remain for up to 6 months. When depot agents are involved, the duration of NMS usually is twice the normal duration.

#### Management

Generally recognized practices in the management of NMS include discontinuation of the offending agent and supportive measures (eg, hydration, cooling measures, antipyretics, monitoring for autonomic instability).

The role of specific pharmacologic agents is debated. Dopamine agonists such as bromocriptine and amantadine are thought to be useful in the treatment of NMS because of the dopamine deficiency hypothesis. Dantrolene, which reduces muscular rigidity, metabolism, and heat generation, also may be used. Some authors report that dopamine agonists, dantrolene, or both in combination may be beneficial in reducing mortality or shortening the duration of illness.<sup>12,13</sup> Other researchers report no benefit and have observed increased complications and prolongation of symptoms following use of these agents.<sup>14</sup> In addition, clinicians should be aware that dantrolene has a significant potential for hepatotoxicity.

Monotherapy with benzodiazepines has been reported to be successful in several cases.<sup>15–17</sup> Recent research by Francis et al<sup>18</sup> revealed benzodiazepines to be highly efficacious in treating NMS as well as in decreasing the duration of NMS by 2 to 3 days.

An interesting model has been proposed in which benzodiazepines increase dopamine activity by indirect actions on the basal ganglia and substantia nigra.<sup>19</sup> An alternative basis for the efficacy of benzodiazepines in NMS derives from the clinical similarity of NMS and catatonia, a condition for which benzodiazepines have been shown to be effective. NMS and catatonia also share a therapeutic response to electroconvulsive therapy.<sup>20–22</sup> The common element between catatonia and NMS may be the role of reduced or blocked dopamine in their pathogenesis.

#### CASE REPORTS

##### Case 1 Presentation

A 48-year-old man was brought to the emergency department (ED) after being found on the street with dilated pupils and hot, dry skin. When the patient was found, his vital signs were as follows: temperature, 105°F; blood pressure, 150/90 mm Hg; pulse, 160 bpm; and

respiratory rate, 40 breaths/min. Two days prior to presentation, the patient was discharged from an inpatient psychiatric unit. He had a history of diabetes mellitus, polysubstance abuse (cocaine, heroin, marijuana), and schizophrenia, which was not reported to emergency medical staff.

On arrival in the ED, the patient was intubated for airway protection and given charcoal, thiamin, 50% dextrose (in water), and naloxone without response. Vital signs were as follows: temperature, 100.8°F; blood pressure, 100/60 mm Hg; pulse, 16 bpm; respiratory rate, 16 breaths/min; and blood glucose, 237 mg/dL. On physical examination the patient's pupils were dilated, his neck was supple, and his lungs were clear bilaterally. He was sedated with intravenous (IV) midazolam and obtunded. His eyes opened to verbal stimuli, and he had positive corneal and gag reflexes. The patient moved all 4 extremities spontaneously. Deep tendon reflexes were normal bilaterally; flexor plantar response was bilateral. In the patient's pocket were found prescriptions for methadone (65 mg orally once daily), paroxetine (20 mg once daily), fluphenazine (5 mg orally twice daily), and benztropine (2 mg orally twice daily).

Laboratory testing revealed a CK level of 321 U/L. Urine drug screen was positive for cocaine. A computed tomography scan of the patient's head revealed frontal atrophy without evidence of mass, bleed, midline shift, or infarct. Electrocardiography revealed a sinus rhythm of 160 and a normal axis without ST or T wave changes. A lumbar puncture was performed and revealed no abnormalities. The patient was started on triple antibiotic coverage, including acyclovir for possible herpes encephalitis, and he was admitted to the intensive care unit for supportive treatment.

On day 2, the patient was still intubated and his CK level had increased to 4620 U/L. His temperature was 101.8°F, blood pressure was 158/80 mm Hg, and pulse was 105 bpm. He was given midazolam as a muscle relaxant and IV lorazepam (2 mg) 2 times for agitation.

The patient's condition stabilized during days 3 to 5. On day 5, his CK level decreased to 1602 U/L, and he was extubated. However, his blood pressure remained elevated, his pulse was greater than 90 bpm, and his temperature was 101°F. Throughout admission, the patient received IV haloperidol (total dose, 2 mg) for agitation. He also became rigid, disoriented, and confused.

On day 6, the patient was referred for psychiatric consultation because he was found wandering around the unit, uncooperative, and very rigid. The patient could speak only Spanish, and the psychiatric interview

was performed via a translator. The patient was disoriented to time and place. His speech was slurred, and his affect was inappropriate. He had auditory hallucinations, and persecutory delusions were elicited. Formal thought disorders include echolalia, perseveration, and loosening of associations. The patient scored 10 out of 25 on the Mini Mental State Examination (MMSE). The patient was diagnosed with NMS, and the psychiatry team recommended discontinuing haloperidol and starting lorazepam (1 mg) orally 3 times daily.

On day 7, the patient was calmer, less rigid, and could comprehend and speak English. He was oriented to time, place, and person and less thought disordered but still complained of having auditory hallucinations and persecutory ideations. He scored 18 out of 30 on the MMSE.

On day 8, the patient was calm, cooperative, and not rigid. He denied auditory and visual hallucinations and did not actively express delusions. No formal thought disorders were found. His MMSE score was 21 out of 30.

On day 9, the patient was discharged to home. The care team recommended that the patient enter a voluntary rehabilitation program, and he and his family agreed.

#### **Case 1 Discussion**

Patient 1 demonstrated all the symptoms of NMS, meeting criteria of the DSM-IV<sup>23</sup> and Caroff et al<sup>24</sup> for diagnosis of NMS. This patient's condition may have been triggered by cocaine exposure or administration of the neuroleptic fluphenazine. Based on the hypothesis that cocaine-associated rhabdomyolysis with hyperthermia and NMS are the same entity, and because NMS and catatonia are related disorders, the patient was treated with lorazepam, which ultimately proved successful.

#### **Case 2 Presentation**

A 91-year-old woman with a history of hypertension and osteoarthritis was admitted to the hospital subsequent to a syncope episode. The patient reported that on the day of admission she lost consciousness for approximately 1 minute. She denied palpitations and head trauma. The patient reported that she had been feeling weak and had a productive cough for 1 week.

Laboratory workup included cardiac assessment, with serial (ie, every 6 hours) CK measurements of 44 U/L, 56 U/L, 61 U/L. Other laboratory test results were within normal limits with the exception of sodium, which was 125 mEq/L. The patient's current medications were

alprazolam (0.5 mg twice daily), atenolol (100 mg 4 times daily), enalapril (20 mg 4 times daily), nifedipine XL (60 mg 4 times daily), nortriptyline (50 mg nightly), and multivitamins (daily).

At 11:00 PM on day 3, the patient was given intramuscular (IM) haloperidol (0.5 mg) because of severe agitation, confusion, and mild delusional ideation. After 15 minutes, another IM dose of haloperidol was administered (1 mg). Three hours later, the patient became stiff, more confused, and had a temperature of 108°F. Her blood pressure was 175/105 mm Hg but after 15 minutes decreased to 75/50 mm Hg. Her CK level was 2676 U/L (ie, 6 hours after the syncope event), and her leukocyte count was  $11.6 \times 10^3/\text{mm}^3$ . A diagnosis of NMS was made. Haloperidol was discontinued, and supportive treatment was initiated.

On day 5, the patient's consciousness remained impaired; she was reactive to pain stimuli and attempted to open her eyes only after several loud commands. She had positive oculocephalic, corneal, and gag reflexes, with no facial asymmetry. Cogwheel rigidity in all extremities was noted. The patient was referred to the consultation liaison service, and she was given a single dose of lorazepam (0.5 mg IV in 50 mL of normal saline) over 1 hour.

On day 6, the patient was less rigid and more oriented. Her CK level decreased to 1046 U/L (a greater than 50% decrease), and her leukocyte count was  $9.4 \times 10^3/\text{mm}^3$ . However, she remained disoriented, expressed mild delusional ideation, and at the end of the day had a temperature of 108°F. The psychiatry team decided to reinstitute lorazepam (0.5 mg orally twice daily).

On day 7, the patient's condition significantly improved; she was more responsive, less delusional, and no longer rigid. Her CK level was 647 U/L, leukocyte count was  $6.7 \times 10^3/\text{mm}^3$ , and vital signs were stable.

#### Case 2 Discussion

This case illustrates classic features of NMS, including generalized muscle rigidity, rhabdomyolysis, fever, altered mental status, autonomic instability, and increasing CK level and leukocyte count following 2 doses of haloperidol (total dose, 1.5 mg). Because of her age and subsequent risk for respiratory arrest, the patient's psychiatry team took precautions and started lorazepam at a very low dose. After the patient appeared to respond to the initial dose of benzodiazepine, the team started lorazepam as a treatment of NMS and achieved favorable results.

#### CONCLUSION

The patients discussed in the preceding case studies were very different, but both presented with classic signs of NMS. Administration of lorazepam appeared to be effective in both patients. The use of benzodiazepines for the treatment of NMS has been suggested in the medical literature. This treatment deserves further assessment to determine whether the addition of benzodiazepines to the treatment protocol for NMS may be warranted. HP

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