

# AANA JOURNAL COURSE

# 4

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## Update for nurse anesthetists Neuroleptic malignant syndrome

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*Neuroleptic malignant syndrome (NMS) is a potentially fatal condition composed of hyperthermia, extrapyramidal symptoms, autonomic nervous system disturbances, and altered levels of consciousness. Although uncertainty exists about its cause, most studies suggest it is the result of dopaminergic deficiency in the central nervous system, most commonly caused by neuroleptic medications.*

*Excessive dopaminergic blockade occurs most commonly in psychiatric patients receiving neuroleptic medications, but many antiemetic medications used in anesthesia also have been implicated. Promethazine (Phenergan), prochlorperazine (Compazine), droperidol (Inapsine), and metoclopramide (Reglan) are most problematic. Reversal of dopamin-*

*ergic blockade in the central nervous system is believed to be the treatment of choice for an acute episode of NMS. Once identified, withdrawal of causative medications, administration of dantrolene or dopamine agonists (bromocriptine and amantadine), and supportive measures will result in a 90% to 94% survival rate from the acute episode.*

*Anesthetists must be aware of the pathophysiology, diagnosis, and treatment of this syndrome. Avoidance of neuroleptic medications, prompt diagnosis, and appropriate treatment will make the difference between success and failure when treating a patient during the acute phase of NMS.*

**Key words:** Malignant, neuroleptic, syndrome.

### Objectives

At the completion of this course, the reader should be able to:

1. Discuss the pathophysiology involved in neuroleptic malignant syndrome (NMS).
2. Identify the patient populations at risk for developing NMS.
3. Describe the differential diagnosis of NMS.
4. Discuss the treatment for NMS.
5. Identify medications to avoid for patients at risk for NMS.

### Introduction

Neuroleptic malignant syndrome (NMS), first recognized in France during the 1960s, is a potentially life-threatening condition caused primarily by neuroleptic medications such as haloperidol, fluphenazine, promethazine, droperidol, and prochlorperazine. Studies have estimated the incidence of NMS to be 0.02% to 3.23% of patients treated with neuroleptics and a mortality rate of 4% to 30%.<sup>1-9</sup> Anesthesia medications may trigger NMS, so it is imperative that anesthetists know which medications to avoid, the

recommended treatment options, and the medications used to treat the syndrome. Awareness of risk factors associated with NMS is important since their avoidance, when possible, may prevent occurrence of the syndrome. Early diagnosis and prompt treatment can make the difference between a successful outcome and death.

### Pathophysiology

Dopaminergic blockade seems to have a central role in NMS. This is based on the fact that most neuroleptics derive their therapeutic effect through blockade of dopamine receptors in the central nervous system (CNS).<sup>10</sup> In fact, cessation of the antiparkinsonian medications levodopa, carbidopa, and amantadine, which replenish dopamine stores in the CNS, might cause a reaction similar to NMS.<sup>5,9,11,12</sup> In addition, an NMS-like condition has been documented in other dopamine-deficient states such as Huntington chorea.<sup>5,12</sup>

Other theories posit that NMS arises from one of the following: (1) a relative imbalance of norepinephrine to dopamine in the CNS, (2) a serotonin imbalance, or (3) excessive catecholamine secretion.<sup>2,3,7,13</sup>

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Since benzodiazepines have shown promise for alleviating some of the signs and symptoms of NMS, research findings also have suggested that NMS involves a  $\gamma$ -aminobutyric acid deficiency.<sup>3,14,15</sup>

### Risk factors

Numerous risk factors related to the development of NMS have been identified. NMS occurs in all age groups, but recent studies have found that elderly people may be at higher risk since they are more likely to have coexisting medical conditions such as nutritional deficiencies, electrolyte imbalances, organic brain syndrome, and dehydration.<sup>3</sup> There does not seem to be a sex-specific trait for NMS.<sup>2</sup> No genetic link has been discovered, but Otani et al<sup>16</sup> reported the cases of a mother and 2 daughters who experienced NMS after exposure to neuroleptics. Suzuki et al<sup>17</sup> found that polymorphism of the dopamine D<sub>2</sub> receptor gene made patients more susceptible. Other risk factors such as physical exhaustion, warm and humid environments, agitation, and dehydration should be minimized or prevented when possible; however, some researchers question whether dehydration is a cause or an effect of the syndrome.<sup>2,4,15,18</sup>

Psychiatric disorders such as schizophrenia and mania involve an excess amount of dopamine. Therefore, many antipsychotic drugs are designed to block dopamine receptors in the CNS. The 5 types of dopamine receptors in the CNS are D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>.<sup>10,19</sup> The antipsychotic potency of neuroleptic medications correlates strongly with their ability to block D<sub>2</sub> receptors, and depot forms (long-acting intramuscular injection) of these medications are associated with a higher incidence of NMS.<sup>2,3,10</sup> The relationship between neuroleptic medications and NMS seems to be correlated positively in a dose-dependent manner.<sup>2-5</sup>

Dopaminergic blockade leading to NMS can occur in the basal ganglia, limbic system, and hypothalamus.<sup>20</sup> Table 1 describes how blockade of dopamine receptors in these areas of the brain can lead to movement irregularities, hyperthermia, autonomic nervous system dysfunction, and mental status changes associated with NMS. Psychiatric patients—especially people with mood disorders, catatonia, and schizophrenia—may be at increased risk for NMS because they are more likely to receive neuroleptic medications.<sup>2,4</sup> Administration of any adjunctive medications such as lithium, monoamine oxidase inhibitors, and tricyclic antidepressants seems to be a precipitating factor for NMS.<sup>2,14,15</sup> Coadministration of haloperidol and lithium poses a particular risk.<sup>3,14</sup> Table 2 provides a summary of commonly prescribed neuroleptics. Newer atypical antipsychotics such as risperidone (Risperdal) inhibit serotonin receptors to a greater extent than do dopamine receptors and show an

**Table 1. Areas of the brain affected by neuroleptic malignant syndrome**

*Basal ganglia:* Involved in motor control and movement.

*Limbic system:* Involved in primitive behavioral responses, emotions, feeding behaviors, and biological rhythms.

*Hypothalamus:* Contains various centers for behavioral drives, has endocrine functions, maintains homeostasis (eg, body temperature regulation), and controls many functions of the autonomic nervous system.

**Table 2. Commonly prescribed neuroleptic medications**

#### Phenothiazines

Chlorpromazine (Thorazine)  
Thioridazine (Mellaril)  
Prochlorperazine (Compazine)  
Promethazine (Phenergan)  
Fluphenazine (Prolixin)  
Promazine (Sparine)

#### Butyrophenones

Haloperidol (Haldol)  
Droperidol (Inapsine)

#### Thioxanthenes

Chlorprothixene  
Thiothixene (Navane)

#### Dibenzepines

Clozapine (Clozaril)  
Olanzapine (Zyprexa)

#### Benzisoxazoles

Risperidone (Risperdal)

increased affinity for D<sub>1</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors than for D<sub>2</sub> receptors; however, they still can cause NMS.<sup>21,22</sup>

Promethazine (Phenergan), prochlorperazine (Compazine), and droperidol (Inapsine) are common neuroleptic medications that exhibit dopamine receptor-blocking effects at the D<sub>2</sub> receptor in the chemoreceptor trigger zone, which leads to their use as antiemetics. Although it is not considered a neuroleptic medication, metoclopramide has antiemetic effects that are due in part to blockade of dopamine receptors in the chemoreceptor trigger zone of the CNS.<sup>23</sup> This ability to block dopamine receptors can precipitate NMS in someone already taking neuroleptic medications, and metoclopramide has been cited in several case reports as providing the mechanism that led to

NMS.<sup>24-26</sup> Pharmacologic prophylaxis for nausea and vomiting may best be achieved in the NMS-susceptible patient population with the use of a serotonin antagonist such as ondansetron (Zofran), dolasetron (Anzemet), or granisetron (Kytril).

### Signs and symptoms

Diagnosis of NMS often is difficult because its manifestations can mimic those of other diseases. Although several researchers have provided suggestions, no universal agreement on diagnostic criteria exists.<sup>2,27,28</sup> Diagnostic criteria established by Caroff and Mann<sup>2</sup> include the following: (1) hyperthermia (temperature, >38°C); (2) muscle rigidity; (3) treatment with neuroleptics within 7 days of onset; (4) 5 of the following: change in mental status, diaphoresis or sialorrhea, tachypnea or hypoxia, tachycardia, hypertension or hypotension, incontinence, elevation of the creatine kinase level, myoglobinuria, leukocytosis, metabolic acidosis, tremor; and (5) absence of drug-induced, systemic, or neuropsychiatric diseases. The current diagnostic criteria as recommended by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, are listed in Table 3.<sup>29</sup>

The signs and symptoms of NMS usually develop during a 24- to 72-hour period and may last from 2 to 30 days after all neuroleptic drugs are discontinued.<sup>5,8,18</sup> The results of studies attempting to predict symptom sequence have been inconclusive.<sup>3,4,15,18</sup> The extrapyramidal reactions associated with NMS are due to dopaminergic blockade in the nigrostriatal pathway.<sup>4,6,14</sup> Affected patients may have tremor, dystonia, catatonia, dyskinesia, bradykinesia, and chorea.<sup>3,8</sup> Profound "lead-pipe rigidity" typically occurs with NMS; however, cases of NMS without rigidity have been documented.<sup>30</sup> Muscle biopsy typically reveals myoedema, myonecrosis, glycogen reduction, and lipid depletion.<sup>2,15,31</sup> A person with NMS also may experience oculogyric crisis (fixed eye position), trismus, dysphagia, and opisthotonos (muscular spasm in which the head is hyperextended and the body is bowed forward).<sup>3,7,11</sup>

Hyperthermia arising from dopaminergic blockade in the hypothalamus may lead to temperatures higher than 41°C.<sup>2,4,5,15,18</sup> Excessive heat also will be generated from extreme muscle rigidity and tetanic contraction for which the body is unable to compensate.<sup>5,15,18,32</sup> As a result, the increased metabolic demand and diversion of oxygen from the myocardium to skeletal muscle may lead to myocardial infarction.<sup>15</sup> Cardiac conduction may be depressed or altered, leading to arrhythmias such as torsades de pointes and cardiac arrest.<sup>2,3,5,8</sup> Autonomic instability, caused by dopamine receptor block-

**Table 3. Research criteria for neuroleptic malignant syndrome\***

- A. The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.
- B. Two (or more) of the following:
  - a. Diaphoresis
  - b. Dysphagia
  - c. Tremor
  - d. Incontinence
  - e. Changes in level of consciousness ranging from confusion to coma
  - f. Mutism
  - g. Tachycardia
  - h. Elevated or labile blood pressure
  - i. Leukocytosis
  - j. Laboratory evidence of muscle injury (eg, elevated CPK levels)
- C. The symptoms in criteria A and B are not caused by another substance (eg, phencyclidine) or a neurological or other general medical condition (eg, viral encephalitis).
- D. The symptoms in criteria A and B are not better accounted for by a mental disorder (eg, mood disorder with catatonic features).

CPK = creatine phosphokinase

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ade in the hypothalamus, frequently leads to alterations in vital signs such as labile blood pressures and tachycardia.<sup>18</sup>

Neurologic manifestations of NMS most commonly manifest as mental status changes and include agitation, stupor, lethargy, and possibly coma.<sup>2,7</sup> More subtle signs and symptoms, such as peripheral neuropathies, mutism, and seizure activity, also might occur.<sup>2,7,33</sup> Dopamine receptor blockade in the reticular activating system is responsible for some of these neurological alterations and may manifest as diffuse slowing of the electroencephalogram.<sup>3,15,22</sup>

Patients with NMS also are at risk for respiratory disturbances secondary to chest wall rigidity and an altered level of consciousness. Respiratory distress may manifest as stridor and tachypnea, while arterial blood gas measurements typically will reveal hypoxia and metabolic acidosis.<sup>2,11,33</sup> Patients with NMS often exhibit sialorrhea and bronchorrhea secondary to autonomic disturbances and are susceptible to aspiration pneumonia. Cases of adult respiratory distress syndrome associated with NMS have been reported.<sup>8,33</sup>

Coagulation abnormalities also might occur in the patient with NMS. Multiple factors, including a hyper-

coagulable state secondary to a labile blood pressure, tissue destruction, hypoxia, acidosis, and ischemia, will attract platelets, initiate the coagulation cascade, and increase the risk of disseminated intravascular coagulation.<sup>15,34</sup>

While no specific laboratory marker is available to test for NMS, an overview of laboratory results will help confirm the diagnosis. The level of creatine kinase—an enzyme normally present in muscle cells—typically is elevated due to muscular damage.<sup>3,4,5,7,15</sup> It is important to note that electrocautery, surgical incision, intramuscular injections, and struggling against physical restraints also might cause an increase in the creatine kinase level.<sup>18,35</sup> Lactic acid dehydrogenase, transaminase, and aldolase levels might be elevated secondary to myonecrosis.<sup>5,15,36</sup> Some researchers have noted an increase in serum catecholamine levels and low serum iron levels due to hemolysis.<sup>2,4,36</sup> Release of myoglobin caused by intense muscle rigidity may lead to myoglobinuria, resulting in renal failure in the absence of adequate hydration. Clinically, this will manifest as reddish brown to cola-colored urine and decreased urine output.<sup>4,7,15,33</sup>

Leukocytosis frequently occurs secondary to stress and tissue damage.<sup>5,7,15,18</sup> Clinicians should be aware, however, that a common side effect of lithium therapy is leukocytosis, and many patients who are taking neuroleptic medications also are receiving lithium, thereby confounding the diagnosis.<sup>15</sup> Generalized electrolyte disturbances are common in NMS. Hypernatremia or hyponatremia, hypocalcemia, hypomagnesemia, and hypophosphatemia occur secondary to intense diaphoresis, incontinence, dehydration, and renal failure.<sup>2,4,15</sup>

### Differential diagnosis

Controversy exists concerning the link between malignant hyperthermia (MH) and NMS, but no reports of NMS have occurred in MH-susceptible patients and vice versa.<sup>6,15,37,38</sup> The list for differential diagnosis is lengthy because it includes any manifestations of fever, encephalopathy, or rigidity, and NMS can mimic many other pathological conditions such as those listed in Table 4.

Of particular interest to anesthesia providers are the similarities between NMS and MH, making diagnosis and appropriate treatment difficult. They share symptoms such as hyperthermia, rigidity, and autonomic nervous system dysfunction; however, important differences exist. MH is triggered by the depolarizing muscle relaxant succinylcholine and all volatile inhalation anesthetics. MH occurs intraoperatively and frequently within minutes to hours, whereas NMS takes days or weeks to develop.<sup>12,15</sup> NMS is more likely to appear postoperatively and is not triggered by anes-

**Table 4. Differential diagnostic considerations for neuroleptic malignant syndrome**

Malignant hyperthermia
Pheochromocytoma
Thyroid storm
Serotonin syndrome
Lethal catatonia
Acute porphyria
Tetany
Encephalitis
Brain lesions and tumors
Sepsis
Heat stroke
Tetanus
Illicit drugs: cocaine, PCP (phencyclidine hydrochloride), Ecstasy (MDMA, 3,4-methylenedioxymethamphetamine)

thetic agents or succinylcholine. MH also is associated with fewer extrapyramidal side effects and a higher creatine kinase level than NMS.<sup>5,12</sup> Unfortunately, while no definitive link between NMS and MH has been established, patients with NMS may be susceptible to MH and should be treated accordingly.<sup>12,39-41</sup> Fortunately, treatment of an acute, fulminant episode of either syndrome focuses on removing the causative factor and administering dantrolene. Continued treatment is substantially different and is the focus of the next section.

### Treatment

Suspicion of NMS should lead to immediate discontinuation of neuroleptic medications.<sup>2-5</sup> After removing the causative medication, the goal of treatment should focus on protecting the patient's airway, preventing hypoxia, supporting systemic perfusion, preventing organ failure, reducing muscular rigidity, and restoring dopaminergic balance in the CNS.<sup>33</sup> Common causes of death in patients with NMS include ventilatory failure, cardiac failure, renal failure, and thromboembolism.<sup>8,9,11,23,33</sup> Patients who have had an acute episode of NMS should be transferred to an intensive care unit for close observation and further management.

Anesthesia providers most commonly will be asked to manage the airway of a patient with NMS. Practitioners must be knowledgeable of medications used to treat NMS, especially dantrolene, which diminishes skeletal muscle contraction, so that temperature and oxygen consumption return to normal within 48 hours.<sup>3</sup> Dantrolene may be given intravenously (2-3 mg/kg) or orally (100-400 mg/d) in divided doses to help alleviate muscular rigidity.<sup>3-5,8,11</sup> Intravenous

administration of dantrolene is preferred to avoid aspiration. Anesthesia providers must monitor patients for excessive muscle weakness, pleural effusion, pneumonitis, pericarditis, hepatitis, nausea, and decreased blood pressure during dantrolene administration since each of these adverse effects has been associated with its use.<sup>11,20,23</sup>

Dopamine agonists, such as bromocriptine and amantadine, are designed to restore the balance of dopaminergic activity in the CNS. Sakkas et al<sup>42</sup> found that dantrolene reduced NMS mortality from 21% to 8.6% and that bromocriptine and amantadine therapy reduced mortality from 21% to 8% and 6%, respectively. Bromocriptine (7.5-60 mg/d) or amantadine (100-400 mg/d) may be given orally or via nasogastric tube in divided doses.<sup>2-5,8,18</sup> Benzodiazepines, such as diazepam and lorazepam, have shown promise for treatment of NMS, although some controversy exists as to their efficacy.<sup>42,43</sup> Modulation of the  $\gamma$ -aminobutyric acid receptor by benzodiazepines may cause an indirect increase in dopamine activity and help to decrease the muscle rigidity associated with NMS.<sup>18</sup> Concomitant benzodiazepine therapy permits administration of a reduced dose of the neuroleptic drug and helps to decrease agitation.<sup>4</sup>

Anticholinergics such as benztropine (Cogentin) are not recommended for reversing the extrapyramidal symptoms and hyperthermia of NMS because they disrupt the dissipation of heat by altering the body's normal thermoregulatory mechanisms.<sup>2,5,8,43</sup> Hyperthermia should be treated with cooling blankets, gastric or colonic lavage, and alcohol baths. The use of antipyretic agents such as acetaminophen is questionable because NMS-induced hyperthermia is not mediated by prostaglandin synthesis.<sup>15,18</sup>

Unresponsive hyperthermia may require the administration of nondepolarizing muscle relaxants to eliminate heat-generating muscle contractions.<sup>15,33</sup> Intubation of the patient will provide airway protection, and neuromuscular blockade will alleviate ventilation problems due to chest wall rigidity.<sup>18</sup> Anxiety secondary to paralysis and mechanical ventilation should be minimized through judicious use of sedation.

Continuous electrocardiographic monitoring is essential to observe for arrhythmias and ischemic changes. Arterial line placement is useful for monitoring fluid and electrolyte balance and coagulation abnormalities. Invasive arterial monitoring also is helpful to monitor labile blood pressures related to NMS. Urine output may be variable due to renal failure and autonomic instability and should be monitored closely with an indwelling urinary catheter. Furthermore, the mannitol contained in dantrolene will lead to diuresis.<sup>23</sup> Immobility places patients with NMS at high risk for deep vein thromboses that can be

prevented with frequent repositioning, low-dose heparin or enoxaparin (Lovenox), antiembolism stockings, and sequential compression devices.<sup>15,18</sup>

Electroconvulsive therapy may be considered for patients with NMS who are physiologically unresponsive to pharmacological and supportive measures. Studies demonstrated an improvement in clinical signs and symptoms and decreased mortality rates in 74% to 83% of patients treated with electroconvulsive therapy.<sup>44,45</sup> It is thought that electroconvulsive therapy works through an increase in the release of dopamine to the CNS.<sup>18</sup> To date, studies have not demonstrated a need to avoid the use of succinylcholine in patients with NMS undergoing electroconvulsive therapy.<sup>5,12,46</sup> However, administration of succinylcholine during electroconvulsive therapy may cause hyperkalemia and subsequent cardiac arrhythmias in a patient with NMS already experiencing rhabdomyolysis or autonomic dysfunction.<sup>43,47</sup>

## Conclusion

Neuroleptic malignant syndrome is a potentially life-threatening disease that must be diagnosed and treated promptly. Although early manifestations might vary, some of the key features for identifying NMS include muscle rigidity, hyperthermia, autonomic nervous dysfunction, extrapyramidal symptoms, and an altered level of consciousness. If the index of suspicion is high, the risk associated with early intervention is minimal compared with the consequences of withholding treatment. Early treatment should include discontinuation of neuroleptic medications. If the syndrome is discovered when it is in a more advanced stage, administration of dantrolene may arrest the episode and bromocriptine or amantadine may prove useful for restoring dopamine balance in the CNS. Monitoring in an intensive care setting will improve the chances of survival for patients recovering from an acute NMS episode.

Because NMS is largely the result of dopaminergic blockade, anesthesia providers should exercise caution when administering medications that have such a mechanism of action, especially to patients with underlying psychiatric disorders and those recently treated with neuroleptic medications. Awareness of this interaction may be crucial to preventing perioperative NMS.

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