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**INTRODUCTION** ð Neuroleptic malignant syndrome (NMS) is a life threatening neurologic emergency associated with the use of neuroleptic agents and characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia.

Mortality results directly from the dysautonomic manifestations of the disease and from systemic complications. Mortality has declined from the earliest reports in the 1960s of 76 percent and is more recently estimated between 10 and 20 percent [1]. This probably reflects greater awareness of the disease, earlier diagnosis, and more aggressive intervention. Requiring a high clinical suspicion for diagnosis and treatment, NMS is appropriately a syndrome more often considered than truly diagnosed.

**EPIDEMIOLOGY** ð Incidence rates for neuroleptic malignant syndrome (NMS) range from 0.02 to 3 percent among patients taking neuroleptic agents [2,3]. This wide range probably reflects differences in the populations sampled, for example, inpatient versus outpatient psychiatric populations, as well as differences in the surveillance methods and definitions of disease used.

While most patients with NMS are young adults, the syndrome has been described in all age groups from 0.9 to 78 years [2,4-6]. Age is not a risk factor [7]. In most studies, men outnumber women twofold. Both age and gender distributions correspond with the distribution of the exposure to neuroleptic agents [4,7].

**ASSOCIATED MEDICATIONS**

**Neuroleptic agents** ð NMS is most often seen with the "typical" high potency neuroleptic agents (eg, haloperidol, fluphenazine) [8-10]. However, every class of neuroleptic drug has been implicated, including the low potency (eg, chlorpromazine) and the newer "atypical" antipsychotic drugs (eg, clozapine, risperidone, olanzapine) as well as antiemetic drugs (eg, metoclopramide, promethazine) [4,11]. Associated medications are listed in the Table (table 1).

While symptoms usually develop during the first two weeks of neuroleptic therapy, the association of the syndrome with drug use is idiosyncratic. NMS can occur after a single dose or after treatment with the same agent at the same dose for many years [12]. It is not a dose-dependent phenomenon, but higher doses are a risk factor [4]. Case-control studies implicate recent or rapid dose escalation, a switch from one agent to another, and parenteral administration as risk factors [1,7,13,14].

**Associated risk factors** ð Case series and case-control studies also suggest that certain psychiatric conditions, acute catatonia, and extreme agitation are over represented in patients who develop NMS [3,13-15]. It is possible that these represent conditions of higher risk simply because of the increased use of higher doses, rapid escalation, and parenteral therapy. Other commonly listed risk factors, concomitant use of lithium or other psychotropic drugs, higher potency agents, depot formulations, comorbid substance abuse or neurologic disease, and acute medical illness (including trauma, surgery, and infection) have not been substantiated in case-control studies [2,4,8,16-18]. It is also

unclear whether dehydration, present in 92 percent of patients, is a risk factor for, as well as an early complication of, NMS [4,19].

**Antiparkinson medication withdrawal** ð NMS is also seen in patients treated for parkinsonism in the setting of withdrawal of L-Dopa or dopamine agonist therapy, as well as with dose reductions and a switch from one agent to another [1,3,20]. Infection and surgery are possible precipitants as well [21]. This may be considered a distinctive disorder from NMS and is sometimes called neuroleptic malignant-like syndrome or parkinsonism hyperpyrexia syndrome as well as acute akinesia or the malignant syndrome in Parkinson disease [21,22]. While some report that the clinical syndrome and laboratory findings are milder and the prognosis is better in this disorder [23], more severe cases and even fatalities have been reported [21,24,25].

**PATHOGENESIS** ð The cause of NMS is unknown. Current theories are limited in their ability to explain all clinical manifestations and in supporting data. An animal model for NMS has been developed, but it does not fully correspond with the human syndrome [26,27].

Because of the class of agents with which NMS is associated, dopamine receptor blockade is central to most theories of its pathogenesis. Central dopamine receptor blockade in the hypothalamus may cause hyperthermia and other signs of dysautonomia [28,29]. Interference with nigrostriatal dopamine pathways may lead to Parkinsonian type symptoms such as rigidity and tremor [16,29]. Other neurotransmitter systems (gamma aminobutyric acid, epinephrine, serotonin, and acetylcholine) also appear to be involved, either directly or indirectly [26,30].

An alternative theory is that rigidity and muscle damage represent a primary effect on the peripheral muscle system, perhaps from direct changes in muscle mitochondrial function [16,31]. This in itself may represent a primary skeletal muscle defect or a direct toxic effect by neuroleptics on skeletal muscle.

A primary role has also been proposed for a disrupted modulation of the sympathetic nervous system, manifesting in increased muscle tone and metabolism and unregulated sudomotor and vasomotor activity leading to ineffective heat dissipation, labile blood pressure and heart rate [31]. In this model, dopamine antagonists precipitate symptoms by destabilizing normal dopamine regulation of efferent sympathetic activity.

Familial clusters of NMS suggest a genetic predisposition to the disorder [32]. Genetic studies have shown that the presence of a specific allele of the dopamine D2 receptor gene is over represented in NMS patients [33]. This allele is associated with reduced density and function of dopamine receptors as well as decreased dopaminergic activity and metabolism.

**CLINICAL MANIFESTATIONS** ð NMS is defined by its association with a class of medications that block dopamine transmission and a tetrad of distinctive clinical features: fever, rigidity, mental status changes, and autonomic instability [3,34].

**Typical symptoms** ð The tetrad of NMS symptoms typically evolves over one to three days. Each feature is present in 97 to 100 percent of patients:

- Mental status change is the initial symptom in 82 percent of patients [35]. It is not surprising, given the usual psychiatric comorbidity of the typical patient, that its significance is often underappreciated. This often takes the form of an agitated delirium with confusion rather than psychosis. Catatonic signs and mutism can be prominent. Evolution to profound encephalopathy with stupor and eventual coma is typical [15].

- Muscular rigidity is generalized and is often extreme. The increased tone can be demonstrated by moving the extremities and is characterized by "lead pipe rigidity" or stable resistance through all ranges of movement. Superimposed tremor may lead to a ratcheting quality or a cogwheel phenomenon. Other motor abnormalities include tremor (seen in 45 to 92 percent), and less commonly, dystonia, opisthotonus, trismus, chorea, and other dyskinesias [2,4]. Patients can also have prominent sialorrhea, dysarthria, and dysphagia.

- Hyperthermia is a defining symptom according to many diagnostic criteria. Temperatures of more than 38ºC are typical (87 percent), but even higher temperatures, greater than 40ºC, are common (40 percent) [4].

- Autonomic instability typically takes the form of tachycardia (in 88 percent), labile or high blood pressure (in 61 to 77 percent), and tachypnea (in 73 percent) [2,19]. Dysrhythmias may occur. Diaphoresis is often profuse.

In an analysis of 340 cases, 70 percent of patients followed a typical course of mental status changes appearing first, followed by rigidity, then hyperthermia, and autonomic dysfunction [35]. Some case reports document delay in the appearance of fever of more than 24 hours, leading to initial diagnostic confusion [2]. There is substantial variability in the presentation of NMS, and other reports do not necessarily substantiate a typical course.

**Laboratory abnormalities**

**Elevated serum CK** ð Laboratory findings often reflect the clinical manifestations of NMS with more severe rigidity leading to more profound creatine kinase (CK) elevation. In NMS, CK is typically more than 1000 IU/L and can be as high as 100,000 IU/L [2,3,16,19,36,37]. Normal CK can be seen if rigidity is not clearly well developed, particularly early in the onset of the syndrome. Elevated CK, particularly in the mild to moderate range, is not specific for NMS and is often seen in patients with acute and chronic psychosis due to intramuscular injections and physical restraints, and sometimes without specific explanation [31,36]. CK levels greater than 1000 IU/L, however, are probably more specific for NMS, and the degree of CK elevation correlates with disease severity and prognosis [2]. A case-control study demonstrated that patients with NMS were more likely to have had elevated CK levels during previous non-NMS admissions than did controls (76 versus 30 percent) [37]. CK levels do usually normalize after an NMS episode.

**Other** ð Other laboratory abnormalities are common but nonspecific.

- A consistent laboratory finding is leukocytosis, with a white blood cell count typically 10,000 to 40,000/mm3 [2,4,19]. A left shift may be present.
- Mild elevations of lactate dehydrogenase, alkaline phosphatase, and liver transaminases are common.
- Electrolyte abnormalities - hypocalcemia, hypomagnesemia, hypo and hypernatremia, hyperkalemia, and metabolic acidosis are frequently observed.
- Myoglobinuric acute renal failure can result from rhabdomyolysis [2,38]. (See "Clinical manifestations and diagnosis of rhabdomyolysis".)
- A low serum iron concentration (mean 5.71 µmol/L; normal 11 to 32 µmol/L) is commonly seen in NMS patients and is a sensitive (92 to 100 percent) but not specific marker for NMS among acutely ill psychiatric patients [19,39].

**Atypical cases** ð There is debate in the literature about milder or atypical cases of NMS. A "forme fruste" of the syndrome has been suggested to occur in milder cases, those associated with lower potency agents, or those diagnosed early on. In particular, rigidity may be milder and perhaps even absent in these situations [40]. While many consider fever to be an essential feature of the diagnosis, cases are reported where it is absent [4]. Complicating this issue is the fact that the isolated appearance of dysautonomia, hyperthermia, Parkinsonian rigidity, and creatine kinase (CK) elevations all occur with antipsychotic therapy. Individually they do not necessarily appear to be a harbinger of NMS [16,41]. From a practical clinical point of view, it seems reasonable to consider the diagnosis when any two of the tetrad of symptoms are present in the setting of an offending agent.

**DIFFERENTIAL DIAGNOSIS** ð The differential diagnosis of NMS can be broadly defined in two categories ï those conditions that are related to NMS and those unrelated to NMS but commonly considered in the differential diagnosis.

**Related disorders** ð NMS is one of a group of acute dysautonomias that share common features: rigidity, hyperpyrexia, and dysautonomia [4,6,40,42]. These entities are usually distinguishable if only by the implicated drugs.

**Serotonin syndrome** ð The most commonly diagnosed related disorder is serotonin syndrome [40,43,44]. This is usually caused by use of selective serotonin reuptake inhibitors and has a similar presentation that is difficult to

distinguish from NMS [17]. Typical features in these patients that are not often seen in NMS patients are shivering, hyperreflexia, myoclonus, and ataxia [45,46]. Nausea, vomiting, and diarrhea are also a common part of the prodrome in serotonin syndrome and are rarely described in NMS. Rigidity and hyperthermia, when present, are less severe than in patients with NMS. (See "Serotonin syndrome".)

**Malignant hyperthermia** ð A rare genetic disorder, malignant hyperthermia is distinguished from NMS by its clinical setting - occurring with use of potent halogenated inhalational anesthetic agents and succinylcholine. Its clinical appearance with hyperthermia, muscle rigidity, and dysautonomia is quite similar to NMS although often more fulminant. Studies using muscle contracture testing to evaluate malignant hyperthermia susceptibility among NMS patients have yielded conflicting results, with some finding a high and others a low prevalence of susceptibility. The test may be unreliable in the setting of acute or recent NMS [16,31,42]. (See "Malignant hyperthermia: Clinical diagnosis and management of acute crisis".)

**Malignant catatonia** ð Most problematic in the differential diagnosis of NMS, malignant catatonia shares clinical features of hyperthermia and rigidity with NMS. However, in this syndrome, there is usually a behavioral prodrome of some weeks that is characterized by psychosis, agitation, and catatonic excitement. The motor symptoms are also characterized by more positive phenomena (dystonic posturing, waxy flexibility, and stereotyped repetitive movements) than are described in NMS [47,48]. Laboratory values are more typically normal. The two disorders can be difficult to distinguish clinically, and historical details, particularly in the typical patient population, can be hard to elicit and interpret. The two syndromes may overlap; many case descriptions exist of NMS arising in patients with malignant catatonia [3,15]. One reviewer found it impossible to distinguish between the two disorders in 22 percent of cases [27]. (See "Catatonia in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Malignant catatonia'.)

**Other drug-related syndromes** ð Withdrawal of intrathecal baclofen therapy has been associated with an NMS-like syndrome in several case reports [49]. In these instances, the increased muscle tone is often described as rebound spasticity rather than rigidity. Otherwise, the spectrum of symptoms appears similar to NMS with dysautonomia, altered sensorium, fever, and elevated creatine kinase (CK) levels. Reduced gamma aminobutyric acid activity is believed to be the pathophysiologic cause. The symptoms reverse with reinstitution of therapy, and benzodiazepines may be helpful.

A central anticholinergic syndrome most often associated with intended or inadvertent drug overdose is better known. Patients present with encephalopathy and elevated body temperatures that are usually not as severe as NMS. Other features seen in NMS (diaphoresis, rigidity, and elevated CK levels) are absent here, while atypical features of NMS (flushing, mydriasis, bladder distension) are common. (See "Anticholinergic poisoning", section on 'Clinical features of overdose'.)

Acute intoxication with certain recreational drugs, especially cocaine and ecstasy (3,4-methylenedioxymethamphetamine, MDMA), can be confused with NMS. Both potent stimulants of the central nervous system, these agents are attractive to abusers because they produce heightened vigilance, energy, and euphoria; however, these same effects can also manifest as psychomotor agitation, delirium, and even psychosis. Hyperthermia and rhabdomyolysis can develop, usually in association with increased physical exertion and ambient temperature. Rigidity is not common in these cases. MDMA use can also cause a serotonin syndrome. These syndromes are discussed in detail separately. (See "MDMA (ecstasy) intoxication" and "Cocaine: Acute intoxication" and "Methamphetamine intoxication".)

**Unrelated disorders** ð Alternative neurologic and medical disorders should be considered in the patient with NMS. Clinical symptoms of these disorders can overlap with NMS, particularly in patients who have extrapyramidal side effects of concomitant neuroleptic use. These diagnoses have serious prognostic and treatment implications and should not be overlooked [9,40]:

- Central nervous system infection (eg, meningitis, encephalitis)
- Systemic infections (eg, pneumonia, sepsis)
- Seizures

- Acute hydrocephalus
- Acute spinal cord injury
- Heat stroke (neuroleptics predispose to heat stroke by impairing thermoregulation)
- Acute dystonia
- Tetanus
- Central nervous system vasculitis
- Thyrotoxicosis
- Pheochromocytoma
- Drug intoxication, toxicity (eg, phencyclidine, ecstasy, cocaine, amphetamines, lithium)
- Withdrawal states
- Acute porphyria

**DIAGNOSIS** ð Although there is no diagnostic test for NMS, testing has a crucial role in the evaluation of patients with potential NMS. Typical laboratory abnormalities help to confirm the clinical diagnosis, some tests rule out other conditions, and others are used to monitor patients for complications of NMS.

In patients with possible NMS, brain imaging studies and lumbar puncture are required to exclude structural brain disease and infection [40]. Magnetic resonance imaging (MRI) and computed tomography (CT) are typically normal. In isolated cases diffuse cerebral edema has been reported in the setting of severe metabolic derangements [50], as well as signal abnormalities in the cerebellum and basal ganglia that are similar to those seen in malignant hyperthermia [51]. Cerebrospinal fluid is usually normal, but a nonspecific elevation in protein is reported in 37 percent of cases [19].

Electroencephalography may be done to rule out nonconvulsive status epilepticus. In NMS patients, generalized slow wave activity is seen [3,19].

An international multispecialty consensus group published diagnostic criteria for NMS in 2011 (table 2) [52]. These are based on positive clinical and laboratory findings as well as the exclusion of alternative causes, each item given a priority score for its relative importance in contributing to the diagnosis. This requires independent validation before its use can be recommended in clinical practice.

**TREATMENT**

**Stop causative agent** ð Removal of the causative agent is the single most important treatment in NMS. Other potential contributing psychotropic agents (lithium, anticholinergic therapy, serotonergic agents) should also be stopped if possible. When the precipitant is discontinuation of dopaminergic therapy, it should be reinstituted.

**Supportive care** ð The need for aggressive and supportive care in NMS is essential and uncontroversial [53]. Complications are common and severe, even fatal. These include:

- Dehydration
- Electrolyte imbalance
- Acute renal failure associated with rhabdomyolysis
- Cardiac arrhythmias including torsades de pointes and cardiac arrest
- Myocardial infarction
- Cardiomyopathy
- Respiratory failure from chest wall rigidity, aspiration pneumonia, pulmonary embolism
- Deep venous thrombophlebitis
- Thrombocytopenia
- Disseminated intravascular coagulation
- Deep venous thrombosis
- Seizures from hyperthermia and metabolic derangements
- Hepatic failure
- Sepsis

The intensive nature of the required monitoring and supportive treatment are such that admission to the intensive care

unit is required. The following supportive treatment should be provided:

- Discontinue any neuroleptic agent or precipitating drug.
- Maintain cardiorespiratory stability. Mechanical ventilation, antiarrhythmic agents, or pacemakers may be required [54].
- Maintain euvolemic state using intravenous fluids. Insensible fluid loss from fever and from diaphoresis should also be considered [55]. If CK is very elevated, high volume intravenous fluids with urine alkalinization may help prevent or mitigate renal failure from rhabdomyolysis [56]. (See "Clinical manifestations and diagnosis of rhabdomyolysis".)
- Lower fever using cooling blankets. More aggressive physical measures may be required: ice water gastric lavage and ice packs in the axilla. The use of acetaminophen or aspirin may have a role in reducing temperature in NMS, but it is not established. (See "Severe nonexertional hyperthermia (classic heat stroke) in adults".)
- Lower blood pressure if markedly elevated. The use of any specific agent over another is not supported by clinical data. Clonidine is effective in this setting [57]. Nitroprusside may have advantages by also facilitating cooling through cutaneous vasodilation [58]. (See "Drugs used for the treatment of hypertensive emergencies".)
- Prescribe heparin or low molecular weight heparin for prevention of deep venous thrombosis. (See "Prevention of venous thromboembolic disease in surgical patients".)
- Use benzodiazepines (eg, clonazepam, lorazepam 0.5 to 1.0 mg) to control agitation, if necessary [27].

**Specific treatments**

**Medical therapy** ð Recommendations for specific medical treatments in NMS are based upon case reports and clinical experience, not upon data from clinical trials. Their efficacy is unclear and disputed [59]. Commonly used agents are dantrolene, bromocriptine, and amantadine.

- Dantrolene is a direct-acting skeletal muscle relaxant and is effective in treating malignant hyperthermia. Doses of 1 to 2.5 mg/kg IV is typically used in adults and can be repeated to a maximum dose of 10 mg/kg/day [60,61]. Efficacy includes reduction of heat production as well as rigidity, and effects are reported within minutes of administration. There is associated risk of hepatotoxicity, and dantrolene should probably be avoided if liver function tests are very abnormal. While some recommend discontinuing it after a few days, others suggest continuing for 10 days followed by a slow taper to minimize relapse [62].
- Bromocriptine, a dopamine agonist, is prescribed to restore lost dopaminergic tone. It is well tolerated in psychotic patients. Doses of 2.5 mg (through nasogastric tube) every six to eight hours are titrated up to a maximum dose of 40 mg/day. It is recommended that this be continued for 10 days after NMS is controlled and then tapered slowly.
- Amantadine has dopaminergic and anticholinergic effects and is used as an alternative to bromocriptine. An initial dose is 100 mg orally or via gastric tube and is titrated upward as needed to a maximum dose of 200 mg every 12 hours.
- Other medications used with anecdotal success include levodopa [29], apomorphine [63], carbamazepine [64], and benzodiazepines (lorazepam or clonazepam) [16,40,65].

The use of any of these medications is controversial and largely unsupported. In an animal model of NMS, dantrolene reduced body temperature, CK levels, and an EMG activation measure of rigidity compared with control [26]. A retrospective analysis of published cases indicates that the use of bromocriptine and/or dantrolene appeared to hasten clinical response [66]. Time to complete recovery was reduced from a mean of 15 days (with supportive care alone) to nine days (with dantrolene) and 10 days (with bromocriptine). Another analysis found reduced mortality: 8.6 percent in

patients treated with dantrolene, 7.8 percent in patients treated with bromocriptine, and 5.9 percent in patients treated with amantadine compared with 21 percent in those receiving supportive care alone [67].

These and similar analyses are of questionable validity because of publication and other biases [1,67]. In contrast, a small prospective study in 20 patients showed that dantrolene and/or bromocriptine use was associated with a more prolonged course (9.9 versus 6.8 days) and a higher incidence of sequelae compared with those receiving supportive care alone [68]. However, the findings in this nonrandomized study could be explained by the fact that patients in the treated group were sicker than those not treated.

While evidence supporting the use of these agents is limited, they are frequently used because of anecdotal evidence of efficacy, lack of other proven treatments, and high morbidity and mortality of the disorder.

**Electroconvulsive therapy** ð The rationale for the use of electroconvulsive therapy (ECT) in NMS includes its efficacy in treating malignant catatonia and reports of Parkinsonism improving with ECT. A further impetus for ECT comes from the frequent need for psychotropic therapy in a setting in which neuroleptics cannot be used.

ECT is a reasonable treatment option in NMS; however, there are no prospective, randomized, controlled data supporting its efficacy. A review of published cases found a lower mortality rate in ECT treated patients compared with those receiving supportive care alone (10.3 versus 21 percent) [69]. In another comprehensive literature review, clinical response occurred after an average of 4.1 treatments. However, interpretation of this is complicated by the variable timing of ECT in relation to symptom onset [70]. While these results are interpreted as supporting ECT use in NMS, methodological issues, including publication bias and lack of randomization preclude conclusions about the efficacy of ECT in NMS.

There are safety concerns for ECT in NMS. Cardiovascular complications occurred in 4 of 55 patients including two patients with ventricular fibrillation and cardiac arrest with permanent anoxic brain injury [70]. Another patient had status epilepticus. Other authors also report uncontrolled spontaneous seizures and aspiration pneumonia complicating ECT treatment for NMS [69-71].

The use of ECT in this setting is further challenged by the requirement for anesthesia. Because of concerns for associated malignant hyperthermia, some authors suggest the use of nondepolarizing agents. However, in over 16 reported cases of NMS patients treated with succinylcholine, there was no malignant hyperthermia [16,70]. Succinylcholine may also cause hyperkalemia and cardiac arrhythmias in patients with rhabdomyolysis and autonomic dysfunction [27].

ECT is generally reserved for patients not responding to other treatments or in whom nonpharmacologic psychotropic treatment is needed. (See "Overview of electroconvulsive therapy (ECT) for adults".)

**PROGNOSIS** ð Most episodes resolve within two weeks. Reported mean recovery times are 7 to 11 days [4,19]. Cases persisting for six months with residual catatonia and motor signs are reported [5]. Risk factors for a prolonged course are depot antipsychotic use and concomitant structural brain disease [71]. Most patients recover without neurologic sequelae except where there is severe hypoxia or grossly elevated temperatures for a long duration.

Reported mortality rates for NMS are 5 to 20 percent [1,5,65,72]. Disease severity and the occurrence of medical complications are the strongest predictors of mortality [40]. A systematic review of published cases before 1989 revealed increased mortality in patients with myoglobinuria and renal failure compared with controls (50 versus 18.8 percent) [1]. Patients with organic brain disease including alcohol and drug addiction had a mortality of 38.5 percent. Others have documented lower mortalities associated with higher potency versus lower potency agents [5] and with atypical compared with typical antipsychotic drugs [72].

**RESTARTING NEUROLEPTICS** ð Patients restarted on neuroleptic agents may or may not have a recurrent NMS episode. It is difficult to quantify this risk from the available data. Different case series with variable duration of follow-up and various use of precautionary measures report relapse rates between 10 and 90 percent [1,4,12,73]. Early resumption of neuroleptic therapy, use of high potency, parenteral neuroleptics, and concomitant use of lithium appear to be risk factors for recurrence [4,73]. Recurrent NMS is also idiosyncratic, with reports of patients with no

sequelae after early resumption of a high potency neuroleptic, and relapses of NMS occurring on low potency agents up to two years later [12,73].

If neuroleptic medication is required, the following guidelines may minimize risk of NMS recurrence [3,19,73]; none of these guarantee either success or failure.

- Wait at least two weeks before resuming therapy, longer if any clinical residua exist.
- Use lower rather than higher potency agents.
- Start with low doses and titrate upward slowly.
- Avoid concomitant lithium.
- Avoid dehydration.
- Carefully monitor for symptoms of NMS.

**SUMMARY AND RECOMMENDATIONS** ð Neuroleptic malignant syndrome (NMS) is a life threatening neurologic emergency associated with the use of neuroleptic agents and characterized by a distinctive clinical syndrome.

- The diagnosis should be suspected when any two of the four cardinal clinical features, mental status change, rigidity, fever, or dysautonomia, appear in the setting of neuroleptic use or dopamine withdrawal. (See 'Clinical manifestations' above.)
- Important considerations in the differential diagnosis include meningitis, encephalitis, systemic infections, heat stroke, and other drug-induced dysautonomias. (See 'Differential diagnosis' above.)
- Diagnostic testing includes tests to rule out these conditions and laboratory evaluation of common metabolic sequelae of NMS, especially elevated CK. (See 'Diagnosis' above.)

**Treatment** ð The management of patients with NMS should be based upon a hierarchy of clinical severity and diagnostic certainty [3,27]:

- When there is any suspicion of NMS, neuroleptic agents should be withheld. Patients should have close inpatient monitoring of clinical signs and laboratory values. (See 'Supportive care' above.)
- Patients with significant hyperthermia and rigidity should be admitted to an intensive care unit setting and undergo aggressive supportive care as outlined above, as well as monitoring for potential dysautonomia and other complications. (See 'Supportive care' above.)
- In patients with CK elevations or hyperthermia on presentation, or who do not respond to withdrawal of medication and supportive care within the first day or two, the use of dantrolene, bromocriptine, and/or amantadine should be considered. (See 'Specific treatments' above.)
- ECT should be considered in patients not responding to medical therapy in the first week, those in whom residual catatonia persists after other symptoms have resolved, and those in whom lethal catatonia is suspected as an alternative or concomitant disorder. (See 'Electroconvulsive therapy' above.)
- Patients restarted on neuroleptic agents may or may not have a recurrent NMS episode. If neuroleptic medication is required, risk may be minimized by following some general guidelines. (See 'Restarting neuroleptics' above.)



## REFERENCES

1. Shalev A, Hermesh H, Munitz H. Mortality from neuroleptic malignant syndrome. J Clin Psychiatry 1989; 50:18.
2. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142:1137.

3. Velamoor VR. Neuroleptic malignant syndrome. Recognition, prevention and management. Drug Saf 1998; 19:73.
4. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am 1993; 77:185.
5. Silva RR, Munoz DM, Alpert M, et al. Neuroleptic malignant syndrome in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999; 38:187.
6. Margetić B, Aukst-Margetić B. Neuroleptic malignant syndrome and its controversies. Pharmacoepidemiol Drug Saf 2010; 19:429.
7. Keck PE Jr, Pope HG Jr, Cohen BM, et al. Risk factors for neuroleptic malignant syndrome. A case-control study. Arch Gen Psychiatry 1989; 46:914.
8. Chandran GJ, Mikler JR, Keegan DL. Neuroleptic malignant syndrome: case report and discussion. CMAJ 2003; 169:439.
9. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007; 164:870.
10. Seitz DP, Gill SS. Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: case reports and a review of the literature. Psychosomatics 2009; 50:8.
11. Kogoj A, Velikonja I. Olanzapine induced neuroleptic malignant syndrome--a case review. Hum Psychopharmacol 2003; 18:301.
12. Pope HG Jr, Aizley HG, Keck PE Jr, McElroy SL. Neuroleptic malignant syndrome: long-term follow-up of 20 cases. J Clin Psychiatry 1991; 52:208.
13. Hermesh H, Aizenberg D, Weizman A, et al. Risk for definite neuroleptic malignant syndrome. A prospective study in 223 consecutive in-patients. Br J Psychiatry 1992; 161:254.
14. Berardi D, Amore M, Keck PE Jr, et al. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case-control study. Biol Psychiatry 1998; 44:748.
15. Koch M, Chandragiri S, Rizvi S, et al. Catatonic signs in neuroleptic malignant syndrome. Compr Psychiatry 2000; 41:73.
16. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. Br J Anaesth 2000; 85:129.
17. Haddow AM, Harris D, Wilson M, Logie H. Clomipramine induced neuroleptic malignant syndrome and pyrexia of unknown origin. BMJ 2004; 329:1333.
18. Nimmagadda SR, Ryan DH, Atkin SL. Neuroleptic malignant syndrome after venlafaxine. Lancet 2000; 355:289.
19. Rosebush P, Stewart T. A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry 1989; 146:717.
20. Wu YF, Kan YS, Yang CH. Neuroleptic malignant syndrome associated with bromocriptine withdrawal in Parkinson's disease--a case report. Gen Hosp Psychiatry 2011; 33:301.e7.
21. Onofrj M, Thomas A. Acute akinesia in Parkinson disease. Neurology 2005; 64:1162.
22. Mizuno Y, Takubo H, Mizuta E, Kuno S. Malignant syndrome in Parkinson's disease: concept and review of the literature. Parkinsonism Relat Disord 2003; 9 Suppl 1:S3.
23. Serrano-Dueñas M. Neuroleptic malignant syndrome-like, or--dopaminergic malignant syndrome--due to levodopa therapy withdrawal. Clinical features in 11 patients. Parkinsonism Relat Disord 2003; 9:175.
24. Sechi GP, Tanda F, Mutani R. Fatal hyperpyrexia after withdrawal of levodopa. Neurology 1984; 34:249.
25. Newman EJ, Grosset DG, Kennedy PG. The parkinsonism-hyperpyrexia syndrome. Neurocrit Care 2009; 10:136.
26. Tanii H, Taniguchi N, Niigawa H, et al. Development of an animal model for neuroleptic malignant syndrome: heat-exposed rabbits with haloperidol and atropine administration exhibit increased muscle activity, hyperthermia, and high serum creatine phosphokinase level. Brain Res 1996; 743:263.
27. Caroff SN, Mann SC, Keck PE Jr. Specific treatment of the neuroleptic malignant syndrome. Biol Psychiatry 1998; 44:378.
28. Boulant JA. Role of the preoptic-anterior hypothalamus in thermoregulation and fever. Clin Infect Dis 2000; 31 Suppl 5:S157.
29. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? Neurology 1981; 31:132.

30. Spivak B, Maline DI, Vered Y, et al. Prospective evaluation of circulatory levels of catecholamines and serotonin in neuroleptic malignant syndrome. Acta Psychiatr Scand 2000; 102:226.
31. Gurrera RJ. Is neuroleptic malignant syndrome a neurogenic form of malignant hyperthermia? Clin Neuropharmacol 2002; 25:183.
32. Otani K, Horiuchi M, Kondo T, et al. Is the predisposition to neuroleptic malignant syndrome genetically transmitted? Br J Psychiatry 1991; 158:850.
33. Mihara K, Kondo T, Suzuki A, et al. Relationship between functional dopamine D2 and D3 receptors gene polymorphisms and neuroleptic malignant syndrome. Am J Med Genet B Neuropsychiatr Genet 2003; 117B:57.
34. Waldorf S. AANA journal course. Update for nurse anesthetists. Neuroleptic malignant syndrome. AANA J 2003; 71:389.
35. Velamoor VR, Norman RM, Caroff SN, et al. Progression of symptoms in neuroleptic malignant syndrome. J Nerv Ment Dis 1994; 182:168.
36. . The myth of elevated serum creatine phosphokinase level and neuroleptic malignant syndrome. Br J Psychiatry 1991; 158:706.
37. Hermesh H, Manor I, Shiloh R, et al. High serum creatinine kinase level: possible risk factor for neuroleptic malignant syndrome. J Clin Psychopharmacol 2002; 22:252.
38. Eiser AR, Neff MS, Slifkin RF. Acute myoglobinuric renal failure. A consequence of the neuroleptic malignant syndrome. Arch Intern Med 1982; 142:601.
39. Lee JW. Serum iron in catatonia and neuroleptic malignant syndrome. Biol Psychiatry 1998; 44:499.
40. Carbone JR. The neuroleptic malignant and serotonin syndromes. Emerg Med Clin North Am 2000; 18:317.
41. Hasan S, Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. Am J Psychiatry 1998; 155:1113.
42. Caroff SN, Rosenberg H, Fletcher JE, et al. Malignant hyperthermia susceptibility in neuroleptic malignant syndrome. Anesthesiology 1987; 67:20.
43. Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. Neurology 1995; 45:219.
44. Ener RA, Meglathery SB, Van Decker WA, Gallagher RM. Serotonin syndrome and other serotonergic disorders. Pain Med 2003; 4:63.
45. Lejoyeux M, Fineyre F, Adès J. The serotonin syndrome. Am J Psychiatry 1992; 149:1410.
46. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991; 148:705.
47. Fleischhacker WW, Unterweger B, Kane JM, Hinterhuber H. The neuroleptic malignant syndrome and its differentiation from lethal catatonia. Acta Psychiatr Scand 1990; 81:3.
48. Castillo E, Rubin RT, Holsboer-Trachsler E. Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. Am J Psychiatry 1989; 146:324.
49. Coffey RJ, Edgar TS, Francisco GE, et al. Abrupt withdrawal from intrathecal baclofen: recognition and management of a potentially life-threatening syndrome. Arch Phys Med Rehabil 2002; 83:735.
50. Blasi C, D'Amore F, Levati M, Bandinelli MC. [Neuroleptic malignant syndrome: a neurologic pathology of great interest for the internist]. Ann Ital Med Int 1998; 13:111.
51. Lyons JL, Cohen AB. Selective cerebellar and basal ganglia injury in neuroleptic malignant syndrome. J Neuroimaging 2013; 23:240.
52. Gurrera RJ, Caroff SN, Cohen A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. J Clin Psychiatry 2011; 72:1222.
53. Prevention and treatment of heat injury. Med Lett Drugs Ther 2003; 45:58.
54. Parry AK, Ormerod LP, Hamlin GW, Saleem PT. Recurrent sinus arrest in association with neuroleptic malignant syndrome. Br J Psychiatry 1994; 164:689.
55. Guzé BH, Baxter LR Jr. Current concepts. Neuroleptic malignant syndrome. N Engl J Med 1985; 313:163.
56. Lappa A, Podestà M, Capelli O, et al. Successful treatment of a complicated case of neuroleptic malignant syndrome. Intensive Care Med 2002; 28:976.
57. Gregorakos L, Thomaides T, Stratouli S, Sakayanni E. The use of clonidine in the management of autonomic overactivity in neuroleptic malignant syndrome. Clin Auton Res 2000; 10:193.

58. Blue MG, Schneider SM, Noro S, Fraley DS. Successful treatment of neuroleptic malignant syndrome with sodium nitroprusside. Ann Intern Med 1986; 104:56.
59. Reulbach U, Dütsch C, Biermann T, et al. Managing an effective treatment for neuroleptic malignant syndrome. Crit Care 2007; 11:R4.
60. Bond WS. Detection and management of the neuroleptic malignant syndrome. Clin Pharm 1984; 3:302.
61. Tsutsumi Y, Yamamoto K, Matsuura S, et al. The treatment of neuroleptic malignant syndrome using dantrolene sodium. Psychiatry Clin Neurosci 1998; 52:433.
62. Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. Neurol Clin 2004; 22:389.
63. Wang HC, Hsieh Y. Treatment of neuroleptic malignant syndrome with subcutaneous apomorphine monotherapy. Mov Disord 2001; 16:765.
64. Thomas P, Maron M, Rascle C, et al. Carbamazepine in the treatment of neuroleptic malignant syndrome. Biol Psychiatry 1998; 43:303.
65. Tural U, Onder E. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome and their association with death. Psychiatry Clin Neurosci 2010; 64:79.
66. Rosenberg MR, Green M. Neuroleptic malignant syndrome. Review of response to therapy. Arch Intern Med 1989; 149:1927.
67. Sakkas P, Davis JM, Janicak PG, Wang ZY. Drug treatment of the neuroleptic malignant syndrome. Psychopharmacol Bull 1991; 27:381.
68. Rosebush PI, Stewart T, Mazurek MF. The treatment of neuroleptic malignant syndrome. Are dantrolene and bromocriptine useful adjuncts to supportive care? Br J Psychiatry 1991; 159:709.
69. Davis JM, Janicak PG, Sakkas P, et al. Electroconvulsive Therapy in the Treatment of the Neuroleptic Malignant Syndrome. Convuls Ther 1991; 7:111.
70. Trollor JN, Sachdev PS. Electroconvulsive treatment of neuroleptic malignant syndrome: a review and report of cases. Aust N Z J Psychiatry 1999; 33:650.
71. Caroff SN, Mann SC, Keck PE Jr, Francis A. Residual catatonic state following neuroleptic malignant syndrome. J Clin Psychopharmacol 2000; 20:257.
72. Nakamura M, Yasunaga H, Miyata H, et al. Mortality of neuroleptic malignant syndrome induced by typical and atypical antipsychotic drugs: a propensity-matched analysis from the Japanese Diagnosis Procedure Combination database. J Clin Psychiatry 2012; 73:427.
73. Susman VL, Addonizio G. Recurrence of neuroleptic malignant syndrome. J Nerv Ment Dis 1988; 176:234.


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## Disclosures

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