BMJ Best Practice

Neuroleptic malignant syndrome

Straight to the point of care

Last updated: Mar 20, 2025

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Summary

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening complication of treatment with antipsychotic drugs, or abrupt withdrawal of dopamine agonists.

Characterized by a tetrad of altered mental status, muscle rigidity, autonomic instability, and hyperthermia.

A diagnosis of exclusion. Common differential diagnoses are sepsis and drug reactions.

NMS is a medical emergency. Treatment consists of immediate cessation of the offending medication (or resumption of the dopamine agonist) and provision of supportive measures (hydration and cooling). Additional treatment may be considered if supportive interventions fail.

A delay of at least 2 weeks in restarting antipsychotic treatment is advised following full resolution of an NMS episode.

Documenting this reaction in the medical records is important.

Definition

NMS is an uncommon, idiosyncratic, life-threatening complication of treatment with antipsychotic medications. NMS has also been associated with use of other psychotropic agents that block central dopamine pathways (e.g., metoclopramide) and with abrupt cessation of dopamine agonists. It is characterized by altered mental state, increased muscle tone or frank rigidity, dysregulated autonomic nervous system, hyperactivity, and hyperthermia.[1] [2] [3] [4] None of these signs are exclusive to this condition, and other important diagnoses (e.g., sepsis) should be excluded first.[5] [6]

This topic covers the diagnosis and management of neuroleptic malignant syndrome in adults.

Epidemiology

The true incidence of NMS is not known because the available evidence is inconclusive.[14] Estimates range from 0.02% to 3%.[15] An important limitation when considering published estimates is that they are almost exclusively incidence proportions (number of new cases over a period of time divided by number of persons at risk at the beginning of the time period) rather than true incidence rates (number of new cases over a period of time divided by the person-time at risk).[14] Reported incidence has declined over the last 20 years, which may reflect greater awareness with heightened vigilance and more prompt clinical intervention. Other possible factors may include systematic reporting bias, an evolving practice trend toward the use of second-generation antipsychotic medications (SGAs), and caution in using high initial doses of antipsychotics.[14]

NMS has been reported to be more common in male than in female patients, but larger studies have not consistently found this.[16] A systematic review and meta-analysis that specifically examined sex and age distribution in NMS found a male to female ratio of 1.5.[17]

Preexisting structural brain abnormality, catatonia, and older age are associated with an increased risk.[3] [18] Mortality associated with NMS appears to vary.[3] [5] [6] [14] [19] [20] [21] Two large studies reported a rate between 8% and 9%.[16] [22] A subsequent systematic review found that respiratory difficulties, hyperthermia severity, and older age were associated with increased mortality.[23]

Risk factors

Strong

exposure to antipsychotic medications

NMS has been reported in association with every antipsychotic medication, presumably through their antagonism of dopamine D2 receptors.[24]

Administration of high doses of antipsychotics at onset of treatment and intramuscular administration may increase the risk.

No single drug is associated with a greater risk than another. Some believe that risk for NMS is less with second-generation antipsychotics (SGAs) than with first-generation antipsychotics (e.g., haloperidol, pimozide), especially high-potency first generation agents. One large case-controlled study found the opposite to be true.[16] Other large studies have found that rigidity is more frequent and mortality is higher with first generation agents.[22] [34]

Almost all patients develop symptoms within 30 days, with 16% developing symptoms within 24 hours after drug initiation and 66% within 1 week.[1] [35]

structural brain abnormality

Preexisting delirium, dementia, brain trauma, Wilson disease, and Parkinson disease appear to be associated with an increased risk for NMS in the context of antipsychotic medications and dopaminergic drug withdrawal.[1] [18] [27] [28] [29]

Weak

abrupt withdrawal of dopaminergic drugs

A syndrome indistinguishable from NMS can occur when dopaminergic drugs (e.g., levodopa, bromocriptine) are abruptly withdrawn.[24] [25] [26]

older age

Structural brain abnormalities associated with advancing age, rather than older age per se, appear to increase risk for NMS.[3] [18]

preexisting agitation

Patients with agitation require antipsychotics to be given intramuscularly.[29] Whether the clinical setting (physical agitation and emotional turmoil) predisposes to the development of NMS is not currently known.

akathisia

Motor restlessness is considered a risk factor for developing NMS.[29]

male sex

A systematic review and meta-analysis that specifically examined sex and age distribution in NMS found that males are approximately 50% more likely to be diagnosed with NMS at any age (male to female ratio of 1.5).[17]

iron deficiency

It has been suggested that low serum iron may contribute to acute hypodopaminergia.[31] [32]

Although acute hypoferremia has been observed in a significant proportion of NMS cases, iron does not readily cross the blood-brain barrier, so it is unlikely that acute changes in serum iron play a causative role in NMS. However, chronically low iron levels could affect brain dopamine function over time.

catatonia

Patients with catatonia may be at risk of progressing to NMS after receiving antipsychotics.[36] [37]

preexisting dehydration

This may be an independent risk factor, secondary to prolonged agitation and/or diaphoresis with poor oral intake, or may be linked by association to sepsis.[29]

exposure to other dopamine antagonists

Some association has been reported with exposure to dopamine antagonists other than antipsychotics, including metoclopramide, lithium, and certain antidepressants.[7] [8] [9]

Etiology

All antipsychotic medications have been associated with NMS, presumably through their antagonism of dopamine D2 receptors.[24] A syndrome indistinguishable from NMS occurs in Parkinson disease in the context of abrupt dopamine agonist withdrawal.[25] [26] Generally, any rapid reduction in dopamine/dopamine agonist availability at postsynaptic receptors increases the risk of NMS, but even long-term dopamine antagonism increases NMS risk.

Predisposing structural brain abnormalities and central nervous system disorders of dopamine (e.g., Parkinson disease, Wilson disease) raise the risk of NMS on exposure to antipsychotic medications.[1] [18] [27] [28] [29] The idiosyncratic nature of its occurrence, and the lack of a reproducible dose-dependent relationship between agent and syndrome, even in individuals known to be at risk for the disorder, has led to speculation that risk is genetic.[30] A number of reports have found statistical associations between NMS and a variety of polymorphisms, but no pattern has emerged.

NMS is also associated with exposure to dopamine antagonists other than antipsychotics, including metoclopramide, lithium, and certain antidepressants.[7] [8] [9]

Pathophysiology

The pathophysiology of NMS has not been established, but an acute imbalance or dysregulation of central nervous system neurotransmitters is strongly suspected.

The ubiquitous dopamine-blocking effects of antipsychotic medications clearly implicate dopamine systems, and it is generally believed that acute, centrally mediated hypodopaminergia leads to muscle rigidity, impaired hypothalamic thermoregulation, and autonomic dysfunction.[18] [24] Limited circumstantial evidence (e.g., alterations in cerebrospinal fluid homovanillic acid in patient case series and reduced dopamine in brain neuroimaging case reports) supports this premise, although these findings are not well replicated.[2] [4]

Abrupt hypoferremia is often present during or immediately preceding the most severe phase of illness, but its significance is not yet clear.[31] [32] Elevated peripheral catecholamines (in particular, norepinephrine) also appear to be relevant to the pathophysiology of NMS, but whether increased sympathetic nervous system activity plays a primary or a secondary role has not been established.[33]

Evidence is less strong for involvement of other neurotransmitters, although occurrence of NMS (as well as serotonin syndrome) with exposure to antidepressant medications has been reported. The involvement of lithium suggests that serotonergic imbalance may perhaps contribute.[1] [3] [9]

Case history

Case history #1

A 60-year-old man with a longstanding diagnosis of schizophrenia presents to the emergency department with recent-onset delirium. He has hyperthermia, tachycardia of 140 bpm, and generalized muscle rigidity. Medication has been recently changed from ziprasidone to perphenazine. Investigations for possible causes, including sepsis, are all normal. He has mild elevation in white blood cell count and elevated serum creatine kinase levels (1200 units/L).

Case history #2

A 26-year-old man with first episode of psychosis, who is highly agitated and has required several intramuscular injections of an antipsychotic medication, has been in seclusion and restraint during the past 24 hours. Nursing staff notice some slurring of speech and unsteadiness of gait. Vital signs are checked and reveal hyperthermia of 104°F (40°C), blood pressure of 180/100 mmHg, and tachycardia

of 110 bpm. He is disoriented to time and place (not to person). The patient also has cogwheel muscle rigidity.

Other presentations

While the typical presentation involves the tetrad of symptoms (altered mental status, autonomic dysfunction, muscle rigidity, and hyperthermia) in the presence of antipsychotics, NMS has also been reported in other circumstances, such as with antidepressant/lithium therapy and withdrawal of dopaminergic drugs.[7] [8] [9]

There is ongoing controversy as to whether mild or incomplete presentations of NMS are "forme fruste" or atypical NMS (e.g., delirium, tachycardia, and muscle rigidity but temperature of <99°F [<37.2°C]).[8] [10] [11] [12] [13]

Recommendations

Key Recommendations

The diagnosis is made in the presence of the tetrad of altered mental status, muscle rigidity, autonomic dysfunction, and hyperthermia. A high index of suspicion leads clinicians to stop antipsychotic medications and institute supportive measures simultaneously with diagnostic evaluation, given the critical nature of this syndrome. This means that less severe cases (partial NMS, mild NMS) may be seen more often than the traditional severe and life-threatening presentations. This also makes the diagnosis more challenging, as many other conditions present with some or all of the features of NMS.

NMS remains a diagnosis of exclusion. A careful assessment, including physical exam and comprehensive tests, is required to exclude other potential causes.[3] [12]

History and physical exam

NMS is more likely to develop following initiation of antipsychotic therapy or an increase in the dose.[1] [5] [28] [39] [40] [41] [42] [43] All antipsychotic medications have been associated with NMS, presumably through their antagonism of dopamine D2 receptors.[24] Almost all patients develop symptoms within 30 days, with 16% developing symptoms within 24 hours after drug initiation and 66% within 1 week.[1] [35]

A prior episode of NMS is generally believed to significantly increase risk for subsequent episodes.

Often it can be difficult to differentiate an acute extrapyramidal reaction from NMS, especially if the prior episode is poorly described in the medical records.[3] [9] [37] [41] [44]

It is useful to ask about a history of delirium, dementia, brain trauma, Wilson disease, or Parkinson disease because they appear to be associated with an increased risk for NMS in the context of antipsychotic use or abrupt withdrawal of dopaminergic drugs.[18] [28] [29]

Key clinical features to make a diagnosis include:

- Altered mental status: characterized by confusion, delirium, or stupor.
- Muscle rigidity: patients can develop muscle rigidity de novo, or worsening of preexisting muscle rigidity. It can be difficult to distinguish these two entities. Generalized rigidity (described as "lead pipe" in its most severe form and usually unresponsive to antiparkinsonian agents) is a cardinal feature. It may be associated with tremor, akinesia, dystonia, trismus, myoclonus, dysarthria, and dysphagia. Patients may have sialorrhea and rhabdomyolysis.[35]
- Hyperthermia: may occur simultaneously with diaphoresis or flushing, indicating a disruption of normal thermoregulatory coordination.
- Autonomic disturbances: may include labile hypertension, tachycardia, tachypnea, urinary incontinence, and diaphoresis.

Tests

Laboratory investigations are essential to exclude other disorders or complications.

- CBC: helpful to rule out sepsis, in conjunction with other clinical parameters.
- Serum creatine kinase (CK) levels: patients with NMS may have significant increases in serum CK indicating muscle injury, with the risk of myoglobinuric acute kidney injury. Subsequent tests should be performed, often daily, until symptoms and laboratory abnormalities resolve.
- Basic metabolic panel (BUN, creatinine): to evaluate the presence of complications such as acute kidney injury, and hydration status.

- Myoglobin levels and urinalysis: myoglobinuria is a poor prognostic sign.
- Urine/blood cultures and chest x-ray may be obtained to rule out sepsis and pneumonia.
- CT/MRI brain scan: to rule out brain infection, mass, or bleed.[12]
- Electroencephalogram: may be needed to rule out status epilepticus.
- Toxicology screen: to exclude drug abuse/overdose/withdrawal.
- Lumbar puncture: to rule out meningitis/encephalitis in patients with high fever, altered mental status, and rigidity.

More specific tests are guided by clinical circumstances.[12] [45]

History and exam

Key diagnostic factors

history of exposure to antipsychotic medications (common)

NMS should generally be diagnosed only in the context of antipsychotic medication administration.[1] [5] [28] [40] [41] [42] However, syndromes resembling NMS have been reported with a variety of medications and intoxications.

Administration of high doses of antipsychotics at onset of treatment and intramuscular administration may increase the risk. All antipsychotic medications have been associated with NMS, presumably through their antagonism of dopamine D2 receptors.[24] No antipsychotic drug is believed to entail more risk than the others, although severity may be less with second-generation antipsychotics than with first-generation antipsychotics.

history of abrupt withdrawal of dopaminergic drugs (common)

NMS can occur when dopaminergic drugs (e.g., levodopa, bromocriptine) are abruptly withdrawn.[24] [26]

altered mental status (common)

Confusion, delirium, stupor.

muscle rigidity (common)

Lead-pipe or generalized hypertonia is a cardinal feature. Generalized rigidity may be associated with tremor, akinesia, dystonia, trismus, myoclonus, dysarthria, and dysphagia. Patients may have sialorrhea and rhabdomyolysis.[35]

autonomic dysfunction (common)

Tachycardia, labile hypertension, diaphoresis, tachypnea, urinary incontinence, pallor.

hyperthermia (common)

Temperature may be quite high and rise so quickly that aggressive external cooling interventions must be applied.

Tests

1st test to order

Test	Result
CBC Increased WBC count is common in NMS, but nonspecific. Increased WBC count can also indicate a differential diagnosis (e.g., sepsis).	WBC count may be elevated
serum creatine kinase High levels may indicate rhabdomyolysis, with myoglobinuria, which may be severe enough to cause acute kidney injury. Creatine kinase is a highly sensitive but nonspecific marker of muscle tissue injury, and may be elevated in many other conditions (e.g., acute alcohol intoxication, acute psychosis). In the absence of known muscle trauma (seizure, prolonged immobility, etc.) the higher the level, the more likely that NMS is present. Subsequent tests should be performed daily for monitoring until resolution.	high levels (>500 units/L); levels above 180,000 units/L have been reported
basic metabolic panel Low sodium, high creatinine, high potassium may indicate differential diagnosis (e.g., acute kidney injury, and hydration status).	usually normal in NMS
brain CT scan Key test in differential diagnosis. May show infection, mass, or bleed.	usually normal in NMS; may reveal potential structural brain abnormality
brain MRI Key test in differential diagnosis. May show infection, mass, or bleed.	usually normal in NMS; may reveal potential structural brain abnormality
myoglobin levels and urinalysis Myoglobinuria is a poor prognostic sign because it may herald multi-organ failure. Urinalysis will help to determine whether a urine myoglobin test is needed (i.e., heme-positive with no red blood cells on microscopy).	myoglobin may be present in urine and/or blood
urine culture To exclude sepsis.	usually normal in NMS
blood culture To exclude sepsis.	usually normal in NMS

Test	Result
lumbar puncture Key test in differential diagnosis. Cloudy cerebrospinal fluid, increased WBC count may indicate central nervous system infection (e.g., meningitis, encephalitis).	usually normal in NMS
toxicology screen To rule out drug misuse/overdose (e.g., ecstasy).	usually normal in NMS
chest x-ray To exclude pneumonia. Some patients with NMS are at increased risk for aspiration.	usually normal in NMS

Other tests to consider

Test	Result
serum iron Acute, transient low levels have been described, and in some cases appear to signal imminent worsening.[31]	low levels
electroencephalogram Status epilepticus may present with behavioral and laboratory features that can be mistaken for NMS.	intermittent or continuous focal or generalized ictal discharges

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Sepsis	• Central nervous system or systemic signs/symptoms of infection. • Sepsis may be the primary diagnosis but may also be present (later in course) as a complication of NMS. Sometimes concurrent infections (e.g., respiratory or urinary tract infection) may further complicate diagnostic assessment.[6] [12] [46]	• Blood, urine, sputum, and other cultures may be positive for infective organisms.
Status epilepticus	• Nonconvulsive status epilepticus is difficult to distinguish clinically from NMS.	• Electroencephalogram may differentiate between status epilepticus and NMS.[47]
Drug misuse/overdose	• History of drug misuse, overdose symptoms.	• Diagnosis is usually based on history and physical exam. Stopping all possible medications, when appropriate, is important.
Catatonia	• Withdrawal, predominance of motor abnormalities, absence of hyperthermia, gradual evolution of presentation, potential history of prior episodes.	• Diagnosis is usually based on history and physical exam.
Serotonin syndrome	• Rapid onset after administration of a serotonergic drug, hyperreflexia, clonus, diarrhea.	• Diagnosis is usually based on history and physical exam.[48]
Mania	• Patients usually present with marked agitation, psychosis, and confusion.	• Diagnosis is usually based on history and physical exam.
Malignant hyperthermia	• Occurs in genetically susceptible people following exposure to anesthetics or depolarizing muscle relaxants, rapid onset, trismus.	• Diagnosis is usually based on history and physical exam.
Heat stroke	• Rapid onset, occurs during episodes of prolonged elevations in ambient temperatures; diaphoresis	• Diagnosis is usually based on history and physical exam, and confirmed by muscle contracture test.

Condition	Differentiating signs / symptoms	Differentiating tests
	and muscle rigidity usually not present.	
Metabolic conditions	• Various metabolic effects (e.g., dehydration, hyponatremia, hypokalemia) can cause delirium presentation.	• Basic and extended metabolic panels (e.g., serum electrolytes, osmolality, serum aminotransferases, and blood glucose) may be abnormal depending on the specific metabolic condition present.
Brain infarcts	• May mimic NMS.	• CT/MRI head may show signs of stroke.
Normal pressure hydrocephalus	• Slowing of gait, urinary urgency, possibly with cognitive impairment. Onset of symptoms is generally insidious (over months to years).	• CT/MRI head may show mild to moderate ventricular enlargement, periventricular leukomalacia, cerebral infarction, relative preservation of cortical gyri and sulci, aqueduct flow void, reduced diameter of the corpus callosum, and widened callosal angle.
Brain tumors	• May mimic NMS.	• CT/MRI head may show evidence of tumor.
Autoimmune encephalitis	• Anti-NMDA receptor encephalitis can mimic psychiatric disorders and prompt treatment with antipsychotic medications. • Patients may have signs and symptoms suspicious for NMS.	• Anti-NMDA-receptor antibodies.

Criteria

Diagnostic and statistical manual of mental disorders (DSM-5-TR)[35]

- Exposure to dopamine antagonist within past 72 hours
- Hyperthermia (>100.4°F [>38.0°C] on at least 2 occasions, measured orally) associated with profuse diaphoresis is a distinguishing feature from other neurologic side effects of antipsychotic medications and other dopamine receptor blocking agents
- Generalized rigidity is a cardinal feature; may be associated with other neurologic symptoms (e.g., tremor, sialorrhea, akinesia, dystonia, trismus, myoclonus, dysarthria, dysphagia, rhabdomyolysis)
- Mental status alteration (delirium or altered consciousness ranging from stupor to coma)
- Creatine kinase elevation (at least 4 times upper limit of normal)

- Autonomic activation and instability, manifested by:
    - Tachycardia (rate >25% above baseline)
    - Blood pressure elevation (systolic or diastolic ≥25% above baseline)
    - Blood pressure fluctuation (≥20 mmHg diastolic change or ≥25 mmHg systolic change within 24 hours)
    - Diaphoresis
    - Urinary incontinence
    - Pallor
- Tachypnea (rate >50% above baseline) is common, and respiratory distress can occur (due to metabolic acidosis, hypermetabolism, chest wall restriction, aspiration pneumonia, or pulmonary emboli) and lead to sudden respiratory arrest.

ICD-11 classification of mental and behavioral disorders[49]

Chapter 8, Diseases of the nervous system; Movement disorders; Certain specified movement disorder (8A07); Other specified movement disorder (8A07.Y).

Recommendations

Key Recommendations

Prompt recognition and treatment is essential. Cessation of the offending medication and provision of supportive medical therapy are the cornerstones of treatment in any suspected case of NMS.[48] Get a toxicology consult or contact the Poison Center for advice. [America's Poison Centers: poison help] Supportive measures (hydration, external cooling if hyperthermia is severe and persistent) should start simultaneously with diagnostic evaluation.

Pharmacologic interventions and electroconvulsive therapy (ECT) are secondary measures, and their role in treating NMS is uncertain. Patients with NMS are usually severely ill and often need to be managed on an ICU or step-down unit.

Ratings scales are available for tracking the clinical course of NMS on the basis of factors such as severity of hyperthermia, rigidity, mental status alteration, and elevation in serum creatine kinase.[50] [51]

Withdrawal of antipsychotic medication

If NMS is suspected, antipsychotics and dopamine antagonists must be stopped, and dopamine agonists must be restored or continued. Other drugs that may be contributory (e.g., lithium, metoclopramide) may need to be stopped.[3] [9] If the patient's psychiatric symptoms compel resumption of antipsychotic medication, a delay of at least 2 weeks following complete resolution of the NMS episode is advisable.[52] In practice, the class of drug that is suspected to be the cause of NMS is usually added to the patient's medical records as an allergy.

Supportive therapy

Oxygen and airway management

- Give supplemental oxygen by nasal cannula if needed; endotracheal intubation may be required for more severe cases.

Hydration

- Most patients are dehydrated in the acute phase of the illness; therefore, administration of fluids, intravenously in severe cases, and prevention of volume depletion are essential.
- When rhabdomyolysis occurs, vigorous hydration with intravenous fluids is recommended to prevent acute kidney injury.

Coolants

- Hyperthermia can be treated with physical cooling measures. Antipyretics do not appear to be effective in NMS.

Patients with dysphagia may require a nasogastric tube for the administration of fluids, nutrition, and pharmacologic therapy.[3]

Pharmacologic therapy

Supportive medical management and prompt cessation of the antipsychotic medication are often sufficient to reverse the symptoms. In more extreme cases, pharmacotherapy can be used to reduce NMS-associated hyperthermia and rigidity. However, there is limited evidence on whether pharmacologic treatments ameliorate symptoms and improve recovery.

There are no specific recommendations regarding sequence or preference of one drug over the other, except that benzodiazepines are generally preferred as first-line treatment because of their lower risk in comparison with bromocriptine and dantrolene.

Benzodiazepines

- Oral or intravenous lorazepam may be helpful to treat NMS-associated agitation and catatonia. It also works as a muscle relaxant. Adverse effects include respiratory depression and/or worsening delirium.[2]

Muscle relaxants

- Dantrolene given orally or intravenously may aid resolution of NMS-associated muscular rigidity and hyperthermia.[48] However, some studies show that combination of dantrolene with other drugs for the treatment of NMS is associated with a prolongation of clinical recovery; therefore, use is somewhat controversial.[38] [53]

Dopaminergic agents

- Bromocriptine and amantadine are especially useful if the NMS was caused by withdrawal of anti-Parkinson medication. They are administered orally or by a nasogastric tube in patients with dysphagia.[2] [3] [18] However, like dantrolene, evidence for a beneficial effect in NMS is equivocal, and their use is also controversial.[38] [53]

Dantrolene, bromocriptine, and amantadine are often used in the treatment of NMS despite the limited evidence of their effectiveness.[1] [37] [38] One systematic case series analysis suggests that dantrolene and bromocriptine may be more effective in the treatment of severe NMS than supportive care alone.[54]

Based on many anecdotal reports, it is generally advised that these treatments be continued until the NMS episode is fully resolved, and possibly longer (e.g., an additional 7-10 days) because NMS can return if effective treatments are terminated prematurely.

ECT

Case reports and one systematic case series analysis suggest that ECT may be effective in the treatment of NMS (particularly if severe), even after failed pharmacotherapy.[54] [55] [56] [57] [58] ECT is considered potentially useful in more extreme cases of NMS, but may often be impractical.

Recurrence and subsequent antipsychotic medication

Recurrence of NMS is managed in the same way as initial presentation: withdrawal of antipsychotic medication, supportive therapy, and adjunctive use of pharmacologic treatments if needed.

- Recurrence of NMS may be less likely if resumption of antipsychotic medication is delayed until 2 or more weeks after resolution of NMS. In practice, this might be difficult to achieve, requiring extreme diligence and seeking additional peer consultation. Vigilance is required in all subsequent antipsychotic medication trials.
- About 2 weeks after resolution of NMS, treatment with an antipsychotic (it is considered prudent to avoid the one that caused NMS) should be initiated at a low dose and slowly titrated in a monitored setting to assess for signs of recurrence.[1] [52]
- Some experts recommend a second-generation agent, with lower risk of extrapyramidal adverse effects, in preference to first-generation antipsychotic medications. However, there is no consensus on this view because no antipsychotic medication has been shown to have more or less risk than another.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute		(summary)
initial episode		
	1st	**withdrawal of antipsychotic medication**
	plus	**supportive therapy**
	consider	**pharmacologic therapy**
	consider	**electroconvulsive therapy**

Ongoing		(summary)
recurrence		
	1st	**retreatment**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

initial episode

1st **withdrawal of antipsychotic medication**

» If NMS is suspected, get a toxicology consult or advice from the Poison Center when reviewing your patient's medication. [America's Poison Centers: poison help] Antipsychotics and dopamine antagonists must be stopped, and dopamine agonists must be restored or continued. Other drugs that may be contributory (e.g., lithium, metoclopramide) may need to be stopped.[3] [9]

» If the patient's psychiatric symptoms compel resumption of antipsychotic medication, a delay of at least 2 weeks following complete resolution of the NMS episode is advisable.[52] In practice, the class of drug that is suspected to be the cause of NMS is usually added to the patient's medical records as an allergy.

plus **supportive therapy**

Treatment recommended for ALL patients in selected patient group

» Give supplemental oxygen by nasal cannula if needed; endotracheal intubation may be required for more severe cases.

» Most patients are dehydrated in the acute phase of the illness; therefore, administration of fluids and monitoring and correction of electrolyte abnormalities are essential. When rhabdomyolysis occurs, vigorous hydration with intravenous fluids is recommended to prevent acute kidney injury.

» Hyperthermia can be treated with physical cooling measures; antipyretics such as acetaminophen or ibuprofen do not appear to be effective in NMS.

» Patients with dysphagia might require a nasogastric tube for the administration of fluids, nutrition, and pharmacologic therapy.[3]

consider **pharmacologic therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

Acute

» lorazepam: 1-4 mg orally/intravenously as a single dose

Secondary options

» dantrolene: consult specialist for guidance on dose

OR

» bromocriptine: 2.5 to 5 mg orally three times daily

OR

» amantadine: 200-400 mg/day orally given in 2 divided doses

» There is limited evidence on whether pharmacologic treatments ameliorate symptoms and improve recovery. There are no specific recommendations regarding sequence or preference of one drug over the other, except that benzodiazepines are generally preferred as first-line treatment because of their lower risk in comparison with bromocriptine and dantrolene.

» Benzodiazepines: oral or intravenous lorazepam may be helpful to treat NMS-associated agitation and catatonia. It also works as a muscle relaxant. Adverse effects include respiratory depression and/or worsening delirium.[2]

» Muscle relaxants: dantrolene given orally or intravenously may aid resolution of NMS-associated muscular rigidity and hyperthermia.[48] However, some studies show that combination of dantrolene with other drugs for the treatment of NMS is associated with a prolongation of clinical recovery; therefore, use is somewhat controversial.[38] [53]

» Dopaminergic agents: bromocriptine and amantadine are especially useful if the NMS was caused by withdrawal of anti-Parkinson medication. They are administered orally or by a nasogastric tube in patients with dysphagia.[2] [3] [18] However, like dantrolene, evidence for a beneficial effect in NMS is equivocal, and their use is also controversial.[38] [53]

» Dantrolene, bromocriptine, and amantadine are often used in the treatment of NMS despite the limited evidence of their effectiveness.[1] [37] [38] One systematic case series analysis suggests that dantrolene and bromocriptine

Acute

may be more effective in the treatment of severe NMS than supportive care alone.[54]

» Caution is advised when using medications in association with NMS. Based on many anecdotal reports, it is generally advised that these treatments be continued until the NMS episode is fully resolved, and possibly longer (e.g., an additional 7-10 days) because NMS can return if effective treatments are terminated prematurely.

consider **electroconvulsive therapy**

Treatment recommended for SOME patients in selected patient group

» Case reports and one systematic case series analysis suggest that electroconvulsive therapy (ECT) may be effective in the treatment of NMS (particularly if severe), even after failed pharmacotherapy.[54] [55] [56] [57] [58] ECT is considered potentially useful in more extreme cases of NMS, but may often be impractical.

Ongoing

recurrence

1st **retreatment**

» Recurrence of NMS is managed in the same way as initial presentation with withdrawal of antipsychotic medication, supportive therapy, and adjunctive use of pharmacologic treatments.

» Recurrence of NMS is less likely if resumption of antipsychotic medication is delayed until 2 or more weeks after resolution of NMS. In practice, this might be difficult to achieve, requiring extreme diligence and seeking additional peer consultation. Vigilance is required in all subsequent antipsychotic medication trials.

» About 2 weeks after resolution of NMS, treatment with an antipsychotic (not the same one that caused NMS) should be initiated at a low dose and slowly titrated in a monitored setting to assess for signs of recurrence.[1] [52] Some experts recommend a second-generation agent, with lower risk of extrapyramidal adverse effects, in preference to first-generation antipsychotic medications. However, there is no consensus on this view because no antipsychotic medication has been shown to have more or less risk than another.

Primary prevention

Judicious use of antipsychotic medications includes:[1] [37] [38]

- Using the lowest effective dose of antipsychotic medication
- Avoiding rapid escalation of antipsychotic medication dosing if possible
- Avoiding concurrent use of multiple medications if possible
- Avoiding abrupt withdrawal of dopaminergic drugs, especially in compromised patients (e.g., Parkinson disease)
- Treating agitation early, using alternatives to antipsychotic medication (e.g., lorazepam) when possible
- Avoiding dehydration.

Secondary prevention

The use and dose of antipsychotic medication should be minimized and agitation treated.

Patient discussions

Patients should be advised to inform clinicians of any previous episode of NMS.

FOLLOW UP

Monitoring

Monitoring

Creatine kinase (CK) levels should be monitored; elevated CK is a sensitive indicator of muscle injury, which may portend subsequent myoglobinuric acute kidney injury. Subsequent tests should be performed, often daily, until symptoms and laboratory abnormalities resolve.

Any NMS reaction should be noted in medical records as a life-threatening adverse drug effect.[1] [3] [14]

Complications

Complications	Timeframe	Likelihood
sepsis	**short term**	**medium**
May occur due to deterioration. Should be managed aggressively.[46]		
acute kidney injury	**short term**	**low**
May occur from dehydration or rhabdomyolysis. Creatine kinase levels and hydration status should be carefully monitored.		
rhabdomyolysis	**short term**	**low**
Progressively high creatine kinase levels and myoglobinuria. Can be fatal. Patients may need dialysis if rhabdomyolysis occurs.[59]		
pulmonary embolism	**short term**	**low**
Secondary to immobility associated with catatonia or rigidity.		
aspiration pneumonia	**short term**	**low**
Secondary to obtundation or dysphagia.		
cognitive deficits	**long term**	**low**
Cognitive impairment has been reported. It is often difficult to distinguish from preexisting cognitive impairment (e.g., dementia, psychosis).[2]		
permanent neurological disability	**long term**	**low**
The nervous system is very vulnerable to injury by hyperthermia, and in cases where body temperature has been extremely high or hyperthermia has persisted for a long time, patients have suffered permanent injury to the central nervous system or peripheral nerves.		
worsening of psychosis	**variable**	**high**
Subsequent medication choices may be limited.		

Prognosis

Some cases of NMS are milder than those in published reports, which may reflect a greater awareness of the risk for this syndrome and more prompt intervention. However, it is possible that NMS manifests in a spectrum of clinical severity.

FOLLOW UP

Mortality associated with NMS appears to vary.[3] [5] [6] [14] [19] [20] [21] Two large studies reported a rate between 8% and 9%.[16] [22] A subsequent systematic review found that respiratory difficulties, hyperthermia severity, and older age were associated with increased mortality.[23]

Recurrence of NMS has been estimated to be as high as 30%, but there are no reliable data regarding recurrence.[3] It is usually recommended that rechallenge be postponed until at least 2 weeks after complete resolution of the syndrome.[52] Rechallenge should proceed slowly and under close monitoring, including appropriate laboratories.[1]

Diagnostic guidelines

Treatment guidelines

Online resources

1. America's Poison Centers: poison help *(external link)*

Key articles

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed, text revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.

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// Acknowledgements:

Dr Ronald J. Gurrera would like to gratefully acknowledge Dr Peter F. Buckley, a previous contributor to this topic.
DISCLOSURES: PFB is on the advisory board (a voluntary, uncompensated role) of the Neuroleptic Malignant Syndrome Information Service. He is also a consultant to Janssen Pharmaceutica and the National Institute of Mental Health (NIMH). He is conducting or has recently conducted research with funding support from AstraZeneca, NIMH, Janssen Pharmaceutica, Pfizer, Solvay, and Wyeth. Previous consultancy and research support has been from Abbott, Alamo Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Lundbeck, Janssen Pharmaceutica, Merck, NIMH, Roche Diagnostics, Pfizer, Solvay, and Wyeth. PFB has no patents or stock in any company. He is an author of several references cited in this topic. PFB is a co-investigator on a study also involving Dr John Lauriello and Dr Daniel R. Wilson, who were reviewers for this topic.