Current PSYCHIATRY

Neuroleptic malignant syndrome: Answers to 6 tough questions

Empiric evidence clarifies risk factors, causes, and first-line interventions

Diagnosis and treatment of neuroleptic malignant syndrome (NMS) are controversial because this potentially life-threatening syndrome is rare and its presentation varies. These factors make it difficult to evaluate treatments in controlled clinical trials, and data about the relative efficacy of specific interventions are scarce. It may be possible, however, to develop rational treatment guidelines using empiric clinical data.[1,2]

This article examines the evidence related to 6 controversial aspects of NMS diagnosis and treatment:

- most-reliable risk factors
- NMS as a spectrum disorder
- what causes NMS
- NMS triggered by first-generation vs second-generation antipsychotics
- first-line interventions
- restarting antipsychotics after an NMS episode.

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1 Are there reliable risk factors for NMS?

In small case-controlled studies, agitation, dehydration, and exhaustion were the most consistently found systemic factors believed to predispose patients taking antipsychotics to NMS (***Table 1, page 96***).[3-5] Catatonia and organic brain syndromes may be separate risk factors.[1,6]

Preliminary studies also have implicated dopamine receptor abnormalities caused by genetic polymorphisms or effects of low serum iron.[1,7,8] Pharmacologic studies have suggested that higher doses, rapid titration, and IM injections of antipsychotics

Neuroleptic malignant syndrome

Clinical Point

For most patients, the benefits of antipsychotics outweigh the risk of NMS

Table 1

What increases NMS risk?

Systemic*
Agitation
Dehydration
Exhaustion
Low serum iron concentrations (normal: 60 to 170 mcg/dL)
Diagnoses
History of NMS
Catatonia
Organic brain syndromes
Central nervous system
Dopamine receptor dysfunction
Basal ganglia dysfunction
Sympathetic nervous system dysfunction
Pharmacologic treatment*
Intramuscular or intravenous injections
High-potency dopamine antagonists
Rapid dose titration
High doses
FGAs compared with SGAs (?)

* For individual patients, these common risk factors must be weighed again the benefits of antipsychotic therapy

FGAs: first-generation antipsychotics; SGAs: second-generation antipsychotics; NMS: neuroleptic malignant syndrome

Source: References 1-5

are associated with increased NMS risk.[3,5] Some studies suggest that 15% to 20% of NMS patients have a history of NMS episodes.[1,2] In addition, high-potency first-generation antipsychotics (FGAs)—especially haloperidol—are assumed to carry higher risk than low-potency drugs and second-generation antipsychotics (SGAs), although this hypothesis remains difficult to prove.[9-11]

These risk factors, however, are not practical for estimating NMS risk in a given patient because they are relatively common compared with the low risk of NMS occurrence. For the vast majority of patients with psychotic symptoms, the benefits of properly indicated antipsychotic pharmacotherapy will outweigh the risks.

2 Is NMS related to parkinsonism, catatonia, or malignant hyperthermia?

Parkinsonism. Some researchers have described NMS as an extreme parkinsonian crisis resulting from overwhelming blockade of dopamine pathways in the brain.[1,2,12] In this view, NMS resembles the parkinsonian-hyperthermia syndrome that can occur in Parkinson's disease patients following abrupt discontinuation or loss of efficacy of dopaminergic therapy, which can be treated by reinstituting dopaminergic agents.[13] Evidence to support this view includes:

- Parkinsonian signs are a cardinal feature of NMS.
- Withdrawal of dopamine agonists precipitates the syndrome.
- All triggering drugs are dopamine receptor antagonists.
- Risk of NMS correlates with drugs' dopamine receptor affinity.
- Dopaminergic agonists may be an effective treatment.
- Lesions in dopaminergic pathways produce a similar syndrome.
- Patients with NMS have demonstrated low cerebrospinal fluid concentrations of the dopamine metabolite homovanillic acid.[14]

Catatonia. Fink et al[15] and others[16-18] have persuasively argued that NMS represents a form of drug-induced malignant catatonia. Evidence supporting this includes:

- The 2 disorders share neuropsychiatric symptoms.
- Catatonic signs are common in NMS.[19]
- Malignant catatonia and NMS share physiologic and laboratory signs.[20]
- Reintroduction of antipsychotics can acutely worsen both conditions.
- Benzodiazepines and electroconvulsive therapy (ECT) are effective treatments for both disorders.[15-18]

Lee[21] examined the relationship between catatonic features and treatment response in 14 NMS patients. Most patients with catatonic symptoms responded to benzodiazepines, whereas none of those did who had an extrapyramidal-hyperthermic presentation without catatonia. Lee concluded that NMS is heterogeneous and may occur

in catatonic and noncatatonic forms that differ in treatment response.

Malignant hyperthermia. Some clinicians have compared NMS with malignant hyperthermia caused by inhalational anesthetics and succinylcholine.[1,2] Evidence includes:

- similar clinical signs of rigidity, hyperthermia, and hypermetabolism
- similar physiologic and laboratory signs, such as rhabdomyolysis
- hyperthermia in both responding to dantrolene.

Although the 2 are similar in presentation, malignant hyperthermia occurs intraoperatively and reflects a pharmacogenetic disorder of calcium regulation in skeletal muscle. Additionally, rigidity in malignant hyperthermia does not respond to peripheral-acting muscle relaxants.[1,22] Evidence suggests that patients who have previously experienced an NMS episode are not at risk for malignant hyperthermia.[22]

3 What is the pathophysiology of NMS?

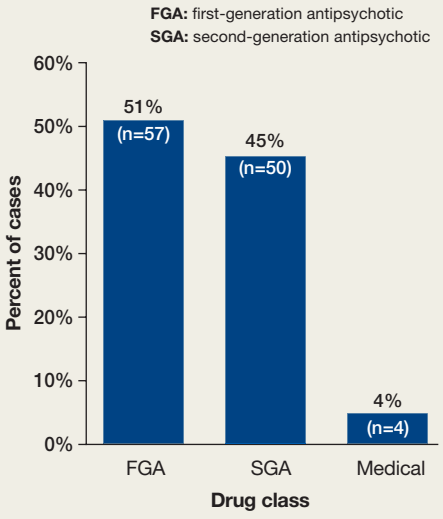
NMS pathophysiology is complex and likely involves interplay between multiple central and systemic pathways and neurotransmitters. As described above, compelling evidence suggests that dopamine blockade plays a central role.[12]

Dopamine blockade in the hypothalamus is believed to contribute to thermoregulatory failure, and blockade in the nigrostriatal system likely contributes to muscle rigidity and hypermetabolism. The loss of dopaminergic input to the anterior cingulate-medial orbitofrontal circuit and the lateral orbitofrontal circuit likely contributes to the mental status changes and catatonic features seen in NMS.[12]

Some researchers have proposed competing or complementary hypotheses, however. For example, Gurrera[23] proposed that patients who are prone to developing NMS have a vulnerability to a hyperactive and dysregulated sympathetic nervous system, and this trait—together with dopamine system disruption induced by dopamine-blocking agents—produces NMS. Other investigators have implicated serotonin, norepinephrine, gamma-aminobutyric acid and glutaminergic mechanisms.[1,12,24,25]

Figure

Which class of antipsychotics is more likely to cause NMS?



Slightly more NMS cases were attributed to FGAs (51%) than SGAs (45%) in an analysis of 111 cases of probable or definite NMS associated with a single drug reported to the NMS Hotline from 1997 to 2006. The FGA haloperidol accounted for 44% of all cases. "Medical" refers to cases in which a neuroleptic was used in a nonpsychiatric setting.

Source: Unpublished data on file at the Neuroleptic Malignant Syndrome Information Service, www.nmsis.org.

4 Are FGAs or SGAs more likely to cause NMS?

NMS is assumed to occur less frequently in patients treated with SGAs than in those receiving FGAs, although this hypothesis is unproven. Isolated reports of NMS have been associated with nearly every SGA.[9-11] It is difficult to prove FGA vs SGA liabilities because:

- NMS is rare.
- Dosing practices may be more conservative now than in the past.
- Most clinicians are aware of the early signs of NMS.

In an epidemiological study of a large

Clinical Point

An analysis of reports to the NMS hotline found haloperidol accounted for 44% of all NMS cases

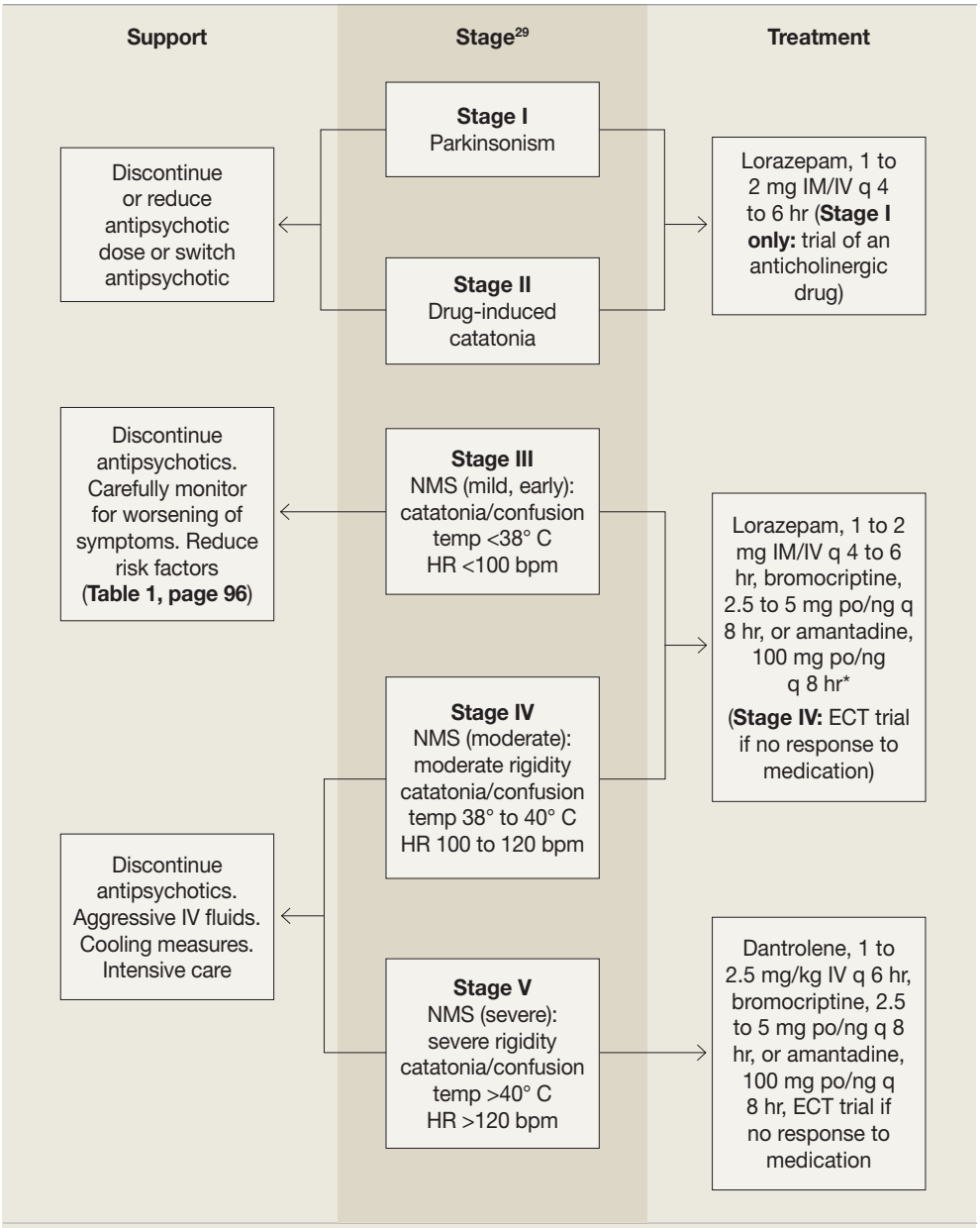
Neuroleptic malignant syndrome

Clinical Point

Lorazepam, 1 to 2 mg parenterally, is a reasonable first-line NMS intervention

Algorithm

Treating NMS based on symptom severity



These recommendations are proposed as a tentative guideline meant for testing in clinical and research settings, and are based only on clinical case reports and literature reviews. Drugs are off-label and not FDA-approved for treating NMS. Doses are estimates based on clinical reports and have not been tested; some clinicians recommend higher doses of lorazepam. ECT may require 6 to 10 bilateral treatments using half-age estimates for initial stimulus settings. ECT may be indicated for patients in Stage IV or V who do not respond to pharmacologic interventions.

ECT: electroconvulsive therapy; HR: heart rate; IM: intramuscular; IV: intravenous; ng: nasogastric; NMS: neuroleptic malignant syndrome; po: by mouth

Source: References 2 (reprinted with permission from the *American Journal of Psychiatry*, © 2007. American Psychiatric Association), 27-29

database, Stubner et al[26] found that patients receiving SGAs had a lower risk of NMS than those treated with haloperidol.[26] In this study, the overall rate of NMS was 0.02%.

NMS hotline data. We recently examined which medication classes were implicated in 111 NMS cases reported to the Neuroleptic Malignant Syndrome Information Service hotline (1-888-NMS-TEMP) between 1997 and 2006 (*Figure, page 97*). We included only cases of definite or probable NMS (as diagnosed by hotline consultants) in which a single

antipsychotic was administered. Slightly more cases were attributed to FGAs (51%) than SGAs (45%). The remaining cases were attributed to neuroleptics used in medical settings (such as promethazine or prochlorperazine).

Because they are now prescribed less often, FGAs accounted for a disproportionate number of NMS cases reported to the hotline. Haloperidol accounted for the majority of FGA cases and 44% of all cases. If we had excluded haloperidol and compared the NMS risk of SGAs to only intermediate- or low-potency FGAs, the relative advantage of SGAs would have been lost. On the other hand, it is clear that SGAs still carry a risk for NMS.

Analyses suggest that the SGA-associated classic features of NMS—fever, muscle rigidity, and autonomic and mental status changes—are retained in patients receiving SGAs, although some may not develop the severe rigidity and extreme temperatures common in patients receiving FGAs.[9-11] The milder clinical characteristics associated with SGAs may reflect more conservative prescribing patterns or increased awareness and earlier recognition of NMS, which would prevent fulminant presentations.

5 What is the evidence for specific NMS treatments?

NMS is rare, its presentation varies, and its progression is unpredictable. These factors make it difficult to evaluate treatments in controlled clinical trials, and data about the relative efficacy of specific interventions are scarce.

Even so, the notion that NMS represents an extreme variant of drug-induced parkinsonism or catatonia suggests that specific NMS treatments could be based on symptom severity or stage of presentation. We propose a treatment guideline based on theoretical mechanisms and anecdotal data (***Algorithm***).[2,27-29]

Support. After immediate withdrawal of the offending medication, supportive therapy is the cornerstone of NMS treatment.[1,2,27]

For patients presenting with mild signs and symptoms, supportive care and careful clinical monitoring may be sufficient. Extreme hyperthermia demands volume resuscitation and cooling measures, intensive medical care, and careful monitoring for complications.

Treatment. Despite a lack of consensus on drug treatments for uncomplicated NMS, approximately 40% of patients with acute NMS receive pharmacologic treatments.[2]

Lorazepam, 1 to 2 mg parenterally, is a reasonable first-line therapy for NMS, especially in individuals with catatonic features.[4,15-18,21,30,31] Some investigators recommend higher doses.[15] Benzodiazepines are preferred if sedation is required in agitated NMS patients.[4,15-18]

Dopaminergic agents such as bromocriptine and amantadine enhance dopaminergic transmission to reverse parkinsonian symptoms and have been reported to reduce time to recovery and halve mortality rates when used alone or in conjunction with other treatments.[13,27,32,33] Rapid discontinuation of these agents can result in rebound symptoms, although this may be true for any specific drug treatment of NMS.[1,31,32]

Dantrolene uncouples excitation-contraction coupling by enhancing calcium sequestration in sarcoplasmic reticulum in skeletal muscle and has been used to treat NMS hypermetabolic symptoms. Some reviews found improvement in up to 80% of NMS patients treated with dantrolene monotherapy.[27,32-35] Compared with supportive care, time to recovery may be reduced—and mortality decreased by almost one-half—when dantrolene is used alone or in combination with other medications.

Not all case reports have shown that dantrolene, benzodiazepines, or dopaminergic agonists are effective in treating NMS.[31,36] In our opinion, only advanced NMS cases—with extreme temperature elevations, severe rigidity, and evidence of systemic hypermetabolism—benefit from dantrolene treatment.[1,2]

ECT has been used successfully to reduce mortality from NMS and other catatonic-spectrum disorders. It is usu-

Clinical Point

Lorazepam, dopaminergic agents, dantrolene, and ECT can reduce recovery time and mortality

Clinical Point

Electroconvulsive therapy is usually tried after supportive therapy and pharmacotherapy are unsuccessful

Table 2

Reintroducing antipsychotics after an NMS episode

Recheck the accuracy of the diagnosis of a previous NMS episode
Document indications for antipsychotic medications
Discuss risks and benefits, including the risk of recurrence, with patient and family
Consider alternate pharmacologic agents
Minimize risk factors (**Table 1, page 96**)
Allow ≥2 weeks (≥4 weeks for long-acting injectable medication) after an NMS episode resolves before rechallenging
Select low-potency FGAs or SGAs
Prescribe an initial test dose
Monitor vital signs and neurologic status
Titrate doses gradually

FGAs: first-generation antipsychotics;
SGAs: second-generation antipsychotics
Source: References 1,2

ally employed after supportive therapy and psychopharmacologic interventions fail.[2,15,16,27,37] ECT for acute NMS typically consists of a series of 6 to 10 treatments with bilateral electrode placement. Daily ECT may be needed initially.[15]

6 Are antipsychotics contraindicated following an NMS episode?

The rate of NMS recurrence on retreatment with an antipsychotic has varied.[38] We estimate that up to 30% of patients may be at risk of NMS recurrence when rechallenged with an antipsychotic.[1] By following proper precautions (*Table 2*), however, you can safely treat most patients who require continued antipsychotic therapy.[1,2]

When you restart treatment, a lower-potency antipsychotic from a different chemical class may be a safer option than retrying the triggering agent, according to retrospective analyses of limited available data. A patient who develops NMS on a FGA might benefit from an SGA trial, although some risk of recurrence remains.[1,10]

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Bottom Line

Neuroleptic malignant syndrome (NMS) may be an extreme variant of drug-induced parkinsonism or catatonia. After immediately withdrawing the offending agent, supportive therapy is the mainstay of management. Benzodiazepines, dopamine receptor agonists, and dantrolene have been used empirically and may reduce time to recovery and mortality. Electroconvulsive therapy may be effective when supportive therapy and pharmacotherapy fail.

Related Resources

- Neuroleptic Malignant Syndrome Information Service. www.nmsis.org.
- Zarrouf FA, Bhanot V. Neuroleptic malignant syndrome: don't let your guard down yet. *Current Psychiatry* 2007;6(8):89-95.

Drug Brand Names

Amantadine • Symmetrel
Bromocriptine • Parlodel
Chlorpromazine • Thorazine
Dantrolene • Dantrium
Fluphenazine • Prolixin
Haloperidol • Haldol
Lorazepam • Ativan
Loxapine • Loxitane
Perphenazine • Trilafon
Prochlorperazine • Compazine, Compro
Promethazine • Phenergan
Thioridazine • Mellaril

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Clinical Point

When restarting antipsychotic therapy in an NMS patient, consider a lower-potency agent from a different class