‘Scared’ and short of breath
Haiwang Tang, MD, PhD, and Xiaohong Hu, MD, MS

While being treated for paranoid schizophrenia, Mr. C, age 42, suddenly develops a fever, high blood pressure, and altered mental status. How would you manage him?

CASE Paranoia and scared
Police bring Mr. C, age 42, to a local crisis center after he is found masturbating in public the same day he was released from jail after serving time for the same behavior. Previously, Mr. C was diagnosed with schizophrenia, paranoid type, and alcohol dependence. He is single, unemployed, and lives with his parents. He has had 3 previous admissions to a psychiatric hospital, but no preexisting medical illness. A judge involuntarily commits Mr. C to our psychiatric facility.

Mr. C looks older than his age and has poor hygiene. He appears bizarre, makes poor eye contact, and speaks slowly but with normal volume. His speech is not coherent, relevant, or goal-directed. He is not able to answer questions properly, chanting “it’s eternity, eternity, eternity.” He shows no tremors, repetitive motor behavior, or muscle rigidity. His affect is flat and he has no suicidal or homicidal ideations. Based on Mr. C’s history, we diagnose him with schizophrenia, paranoid type and alcohol dependence.

Over the next 9 days, Mr. C receives trials of haloperidol, lorazepam, diphenhydramine, ziprasidone, olanzapine, hydroxyzine, trazodone, and benztrapine to treat his schizophrenia. From days 1 to 3, all medications are given on an as-needed basis. On day 1, Mr. C receives haloperidol, 20 mg, lorazepam, 9 mg, diphenhydramine, 150 mg, and ziprasidone, 20 mg. On day 2, he receives haloperidol, 15 mg, lorazepam, 10 mg, olanzapine, 20 mg, hydroxyzine, 100 mg, and trazodone, 50 mg. On day 3, he receives haloperidol, 20 mg, lorazepam, 6 mg, and trazodone, 100 mg. On days 4 to 8, in addition to scheduled haloperidol, 30 mg/d, benztrapine, 1 mg/d, and trazodone, 100 mg/d, he receives haloperidol, 5 mg, and lorazepam, 2 mg, as needed. On day 9, he receives the scheduled haloperidol, 30 mg/d, benztrapine, 1 mg/d, and trazodone, 100 mg/d.

During his stay, Mr. C is incoherent and disorganized. On day 9, he eats all of his lunch, none of his dinner, but sips milk and juice and eats snacks. He drinks 2 small cups of water with medication and 2 small cups of water during oral care. His mucosa and tongue are dry. At 11:30 PM, while lying in bed mumbling “scared, scared,” he experiences shortness of breath. His temperature is 99.6°F, blood pressure is 151/93 mm Hg, pulse is 125 beats per minute, respiratory rate is 40 breaths per minute, and oxygen saturation is 91% on ambient air. Twenty minutes later, his blood pressure increases to 180/120 mm Hg. On physical examination, he has “lead pipe” rigidity of both arms. He is awake, confused, and not able to communi-

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Mr. C's blood pressure and pulse changes from day 4 to day 9 in the psychiatric hospital

The authors' observations

NMS is a life-threatening, iatrogenic neurologic emergency associated with antipsychotic use. Early incidence rate estimates ran as high as 3% of patients treated with antipsychotics; however, more recent data suggest an incidence of 0.01% to 0.02%.\(^1\) This decrease in frequency likely reflects increased awareness of the disorder, more conservative prescribing patterns, and a shift to using atypical antipsychotics.\(^2\) In the mid 1980s and early 1990s the mortality rate was 25% to 30% if NMS was not promptly recognized and treated\(^3\); however, progression to more fulminant, lethal NMS episodes now occurs less often and the mortality rate ranges from 10% to 20%.\(^4\)

If NMS is suspected, immediate transfer to an emergency department (ED) is necessary. Even with early diagnosis, however, complications of NMS are still likely, including:

- rhabdomyolysis
- renal failure
- seizures
- respiratory failure
- aspiration pneumonia
- disseminated intravascular coagulation
- venous thromboembolism.\(^5\)\(^9\)

Caroff et al reported observing a residual catatonic state after acute NMS symptoms subsided.\(^10\)

Although the pathophysiology of NMS is complex—involving a cascade of dysregulation in multiple neurochemical and neuroendocrine systems—dopamine blockade likely plays a pivotal role in trig-
gating the condition. In addition, evidence supports the hypothesis that dysregulated sympathetic nervous system hyperactivity is responsible for most NMS features.

**TREATMENT**

**Arrival in the ED**

Based on his elevated blood pressure (151/93 mm Hg), “lead pipe” rigidity, and increased body temperature associated with Mr. C’s history of haloperidol use for 9 days, the treatment team suspects NMS. Labile blood pressure, which changed from 151/93 to 180/120 mm Hg in 20 minutes, reinforces the NMS diagnosis. Approximately 30 minutes after Mr. C shows signs of NMS, he is transferred to a local ED. He is awake, alert, and communicative after he arrives in the ED, but becomes confused and noncommunicative the next morning. When he arrives in the ED, he is found to have tachycardia (114 beats per minute), tachypnea (26 breaths per minute), blood pressure of 132/84 mm Hg, and temperature of 102°F. In the ED, he is given IV normal saline, diphenhydramine, 25 mg, and IV lorazepam, 1 mg. His rigidity slightly improves.

Early the next morning, his blood pressure is 182/89 mm Hg, respirations are 30 to 40 breaths per minute, and heart rate is 120 beats per minute. He then receives IV lorazepam, 2 mg, after which his tachypnea, tachycardia, and elevated blood pressure improve.

**Which is not a risk factor for NMS in a patient taking an antipsychotic?**

- a) lithium use
- b) depot neuroleptic use
- c) male sex
- d) female sex
- e) dehydration

**The authors’ observations**

A case-control study by Keck et al comparing 18 patients with NMS and 36 matched neuroleptic-treated patients with no history of the syndrome identified greater psychomotor agitation, significantly high-
er doses of neuroleptics, greater rates of dosage increase, and a greater number of IM injections as potential risk factors. Other potential risk factors include use of restraints, pre-existing CNS dopamine activity or receptor function abnormalities, and iron deficiency. Agitation, dehydration, and exhaustion were found to be the most consistent systemic factors predisposing patients taking antipsychotics to NMS in small case-control studies. Well-supported risk factors also include use of high-potency antipsychotics, prior episodes of NMS, age <40, male sex, malnutrition, organic brain syndromes, and lithium use.

There is no way to predict the risk of NMS for an individual patient. Usually, symptoms develop within 4 weeks of starting an antipsychotic, but can occur after taking the same dose for many months.

Mr. C’s risk factors include high-potency antipsychotic use, male sex, relatively high dose (haloperidol, 30 to 35 mg/d), agitation, dehydration, and exhaustion.

Managing NMS

The standard approaches for managing patients with NMS include discontinuing suspected triggering drugs and providing supportive care. Beyond supportive care, oral or IV benzodiazepines may relieve symptoms and speed recovery. Dopaminergic drugs, such as bromocriptine or amantadine, used alone or with other treatments, can reduce parkinsonism and disease duration and mortalit-
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Case that Test Your Skills

**Table 1**

<table>
<thead>
<tr>
<th>DSM-IV-TR criteria for neuroleptic malignant syndrome</th>
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<tbody>
<tr>
<td>A. The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication</td>
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<tr>
<td>B. 2 (or more) of the following:</td>
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<tr>
<td>• diaphoresis</td>
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<tr>
<td>• dysphagia</td>
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<tr>
<td>• tremor</td>
</tr>
<tr>
<td>• incontinence</td>
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<tr>
<td>• changes in level of consciousness ranging from confusion to coma</td>
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<tr>
<td>• mutism</td>
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<tr>
<td>• tachycardia</td>
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<tr>
<td>• elevated or labile blood pressure</td>
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<tr>
<td>• leukocytosis</td>
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<tr>
<td>• laboratory evidence of muscle injury (eg, elevated creatine kinase)</td>
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**Table 2**

<table>
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<tr>
<th>Diagnostic features of neuroleptic malignant syndrome</th>
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<tr>
<td>Essential features: severe muscle rigidity and elevated temperature in an individual using neuroleptic medication</td>
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<tr>
<td>Elevated temperature: from mild (eg, 99° to 100°F) to markedly hyperthermic states (eg, 106°F)</td>
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<tr>
<td>Creatine kinase: typically elevated, ranging from minor elevations to extremely high levels (exceeding 16,000 IU)</td>
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<td>Other features: mental status changes, unstable blood pressure, diaphoresis, other signs of autonomic dysfunction</td>
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**Clinical Point**

ECT may be effective for NMS patients who do not respond to supportive care and drug therapy.

**OUTCOME** Improvement, discharge

Mr. C is admitted to the hospital with the diagnosis of NMS and transferred to the intensive care unit (ICU) for treatment. After Mr. C is admitted to the ICU, apart from continuing the medication given in the ED, he also receives dantrolene, 2 mg/kg, then 1 mg/kg, 4 times a day, as well as IV lorazepam, 1 mg every 6 hours. His other medications include IV pantoprazole, 40 mg/d, for prophylaxis of stress ulcer. Diphenhydramine administration is changed to as needed. On the second day in the ICU, he has only mild upper extremity rigidity but no lower extremity rigidity. However, he suffers 1 seizure, which is treated with IV fosphenytoin at the loading dose, 18 mg/kg, then a maintaining dose of 5 mg phenytoin equivalent/kg/d.

Mr. C remains in the ICU for 7 days. There he receives valproic acid, titrated to 500 mg in the morning and 1,000 mg at bedtime, for agitation. He also receives olanzapine, 5 mg/d, for psychotic symptoms. He develops deep vein thrombosis in the right cephalic vein, which is treated with subcutaneous enoxaparin, 1 mg/kg, and warfarin, 5 mg/d. For a detailed description of Mr. C’s creatine kinase, blood pressure, and temperature while in the ICU, visit this article at CurrentPsychiatry.com.

He is discharged from the hospital after 2 weeks and returns to the psychiatric facility. He continues to be treated for paranoid schizophrenia with olanzapine, 5 mg/d.

Which of the following medications has not been reported to cause NMS?

- quetiapine
- aripiprazole
- clozapine
- ziprasidone
- none of above

**The authors’ observations**

High-potency, typical antipsychotics can cause NMS, as shown in Mr. C’s case. It also can be caused by typical low-potency antipsychotics, atypical antipsychotics.
Cases That Test Your Skills

Clinical Point

NMS can be caused by typical or atypical antipsychotics, antiemetic drugs, and lithium.

antiemetic drugs, and lithium, and can occur after the withdrawal of levodopa and similar dopaminergic agents during Parkinson’s disease treatment. Atypical antipsychotics reported to be associated with NMS include clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, and paliperidone. Atypical antipsychotic-induced NMS also has been reported in children and adolescents.

With the broad application of atypical antipsychotics, physicians should be aware of atypical NMS presentation. Although NMS diagnosis commonly requires core symptoms of hyperthermia and muscle rigidity (Tables 1 and 2, page 79), atypical presentations may not demonstrate temperature changes and/or muscle rigidity or may progress slowly over several days, leading to a delay in diagnosis and treatment. Therefore, clinicians should evaluate any patient taking antipsychotics for features of NMS and not prematurely exclude a NMS diagnosis in cases where severe rigidity or hyperthermia is not initially apparent.

References

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- Logistics and staffing for TMS in the office setting
- Identifying patients who can benefit from TMS
- Presenting TMS to patients

Introduction by

Philip G. Janicak, MD • Rush University Medical Center, Chicago, Illinois
Neuroleptic malignant syndrome (NMS) is a life-threatening condition associated with antipsychotic use. Hallmark symptoms include muscle rigidity and elevated body temperature, but these symptoms may be absent in atypical cases. Be vigilant for possible NMS in all patients taking antipsychotics.

Related Resource

Drug Brand Names
- Amantadine • Symmetrel
- Aripiprazole • Abilify
- Benztropine •Cogentin
- Bromocriptine • Parlodel
- Clozapine • Clozaril
- Dantrolene • Dantum
- Diphenhydramine • Benadryl
- Enoxaparin • Lovenox
- Fosphenytoin • Cerebyx
- Haloperidol • Haldol
- Hydroxyzine • Vistaril
- Levodopa • Sinemet
- Lithium • Eskalith, Lithobid, others

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Clinical Point
Atypical NMS presentations may not demonstrate temperature changes or muscle rigidity or may progress slowly over several days.
Mr. C’s creatine kinase level (IU/L) during the first 5 days in the intensive care unit

Mr. C’s blood pressure before and after admission
Mr. C’s temperature before and after admission

Figure 5