Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

Mr. M has symptoms of neuroleptic malignant syndrome. For years, he has been taking antipsychotics without suffering complications. What caused his acute episode?

Did antismoking therapy make him sick?

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PRESENTATION UNCONSCIOUS ON THE STREET

Emergency medical personnel bring Mr. M, age 66, to the ER after passers-by find him supine on the sidewalk. On arrival, he is comatose as confirmed by a Glasgow Coma Scale score of 8 (eye opening 3, verbal response 2, motor response 3). Systolic blood pressure is 108 mm Hg on palpation, pulse is 135 beats per minute, and temperature is 105 °F. Minor abrasions cover his face and arms, and his hands and feet are rigid.

Mr. M has lived at a board-and-care facility for 30 years. The facility's operator tells us that Mr. M has had schizophrenia for 40 years and has been taking:

- olanzapine, 7.5 mg each morning and 10 mg at bedtime
- chlorpromazine, 50 mg nightly
- lithium carbonate, 300 mg tid
- and benztropine, 2 mg bid.

For years, Mr. M had taken chlorpromazine, 600 mg/d, without suffering adverse effects. Six weeks before the patient presented to us, his outpatient psychiatrist added standard-release bupropion, 150 mg each morning, to help him quit smoking and improve his mood. Mr. M's boarding facility caregivers say that earlier today, he had seen the psychiatrist for a routine visit. The psychiatrist did not change his medication.

Three weeks ago, Mr. M was hospitalized for 6 days with pneumonia. In 3 months, he will undergo surgery for prostate cancer. He is taking no medication for the prostate cancer.

Creatine phosphokinase (CPK) is 2,939 IU/L, indicating neuroleptic malignant syndrome (NMS). Other laboratory test results suggest diabetes or renal failure (*Table 1*). Lumbar puncture shows protein at 91 mg/dL, glucose at 74 mg/dL, and red- and white-blood-cell counts at 0 and 1, respectively. CSF Gram's stain and brain CT are unremarkable. ECG is normal except for sinus tachycardia. Serum lithium is normal (1.1 mmol/L).

Mr. M undergoes tracheal intubation and receives ceftazidime, dose unknown, because chest radiograph shows lower lung opacities, suggesting aspiration. He receives morphine, 2 to 4 mg hourly as needed, to calm him during intubation. He is then transferred to the intensive care unit.

Mr. M's presenting symptoms and recent history suggest:
a) seizure
b) NMS
c) infection
d) delirium caused by pneumonia

Table 1

Diabetes, renal failure, or NMS? The story behind Mr. M's laboratory values

	Mr. M's reading	Normal range	Might suggest
CPK	2,939 IU/L	8-150 IU/L	NMS
Serum creatinine	1.9 mg/dL	0.6-1.5 mg/dL	Renal failure, a complication from elevated CPK
Serum glucose	143 mg/dL	66-99 mg/dL	Diabetes mellitus

NMS: Neuroleptic malignant syndrome
CPK: Creatine phosphokinase

The authors' observations

NMS, a potentially fatal side effect of antipsychotics, is characterized by rigidity, hyperthermia, and autonomic instability[1]—as seen with Mr. M.

The patient's rigidity, elevated creatine kinase, and face and arm abrasions could suggest a seizure. Mr. M's EEG is negative, however, and he has no history of seizures or head trauma, so seizure is ruled out.

Researchers have associated bupropion with a small risk of developing seizures. Richmond and Zwar[2] reported a 0.1% risk with bupropion, ≥300 mg/d, but Mr. M was taking 150 mg/d. Dunner et al[3] estimated the risk of developing seizure while taking standard-release bupropion—the form Mr. M used—at 0.06%, but patients in this study who developed seizures typically had a past seizure disorder or head trauma.

The combination of hyperthermia, tachycardia, altered mental status, and positive chest X-ray suggest pneumonia, which was addressed with antibiotics. Pneumonia, however, does not solely account for Mr. M's fever, rigidity, and profoundly increased CPK. These findings suggest NMS.

The Glasgow Coma Scale (GCS) is used to quantitatively rate degree of responsiveness in critically ill or injured patients *(Table 2, page 94)*. Total scores range from 3 to 15 based on the patient's best eye, motor, and verbal responses. Total score ≤8 indicates a probable coma. Serial GCS scores can measure clinical course in comatose patients.

TREATMENT SLOW PROGRESS

In the ICU, we diagnose NMS and stop all psychotropics, fearing that interactions between any of them might be causing NMS. We give midazolam, 1 to 2 mg hourly as needed for agitation, and continue morphine, 2 to 4 mg hourly as needed for pain. We stop ceftazidime after ruling out aspiration risk.

On day 2 of hospitalization, we call the neurology and consultation-liaison (C-L) psychiatry services. The C-L psychiatrist attempts a mental status examination, but Mr. M is too frail and sedated to communicate. Neurologic exam shows increased foot rigidity, and follow-up studies show negative EEG, normal head and neck MRIs and MRAs, a peak in CPK at 5,487 IU/L, and normal chest films.

We taper and discontinue midazolam and morphine, and Mr. M's consciousness improves as the dosages decrease. We add lorazepam, 1 mg tid, to address Mr. M's agitation. He also starts physical therapy to address potential movement problems caused by laying static for 3 days. By day 7, he is extubated and transferred to the general medical unit.

On day 9, Mr. M's recall and concentration are diminished, and he cannot follow a 3-step command. His Mini-Mental State Examination (MMSE) score of 17 points to a cognitive impairment.

continued

Table 2

Using Glasgow Coma Scale to determine level of consciousness

Component	Response	Score
Best eye response	No eye opening	1
	Eye opening to pain	2
	Eye opening to verbal command	3
	Eyes open spontaneously	4
Best verbal response	No verbal response	1
	Incomprehensible sounds	2
	Inappropriate words	3
	Confused	4
	Oriented	5
Best motor response	No motor response	1
	Extension to pain	2
	Flexion to pain	3
	Withdrawal from pain	4
	Localizing pain	5
	Obeys commands	6

Total score ≤8 is severe, and 90% of patients with scores ≤8 are in a coma). Coma is defined as not opening eyes, not obeying commands, and not saying understandable words. Composite scores listing eye, verbal, and motor responses (such as E3V3M5) are clinically more useful than totals.

Source: Reprinted from Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;304(7872):81-4, with permission from Elsevier.

By day 12, residual psychosis is increasing Mr. M's confusion, paranoia, and agitation. Despite this complication, he is able to work with his occupational and physical therapists.

By day 20, Mr. M becomes more paranoid, with tangential and loose associations. To address these symptoms, we stop lorazepam and start aripiprazole, 15 mg each morning. Because aripiprazole is a partial dopamine agonist and antagonist, it is less likely than other antipsychotics to cause recurrence of NMS symptoms.

Four days later, Mr. M is medically cleared for transfer to the county psychiatric hospital. Creatinine and CPK elevations, metabolic acidosis, and anemia have resolved.

TREATMENT NEW FACILITY, NEW DRUGS

On initial evaluation at the psychiatric hospital, Mr. M is cooperative and aware of person, place, and time. His thought processes range from tangential to disorganized, and his paranoia persists.

The attending psychiatrist stops aripiprazole and starts risperidone, 1 mg bid, possibly because he is less familiar with aripiprazole—a newer antipsychotic—than with risperidone. Laboratory results within 3 days of starting risperidone show normal serum levels, blood counts, liver enzymes, and CPK.

On day 2 at the psychiatric hospital, Mr. M's behavior worsens; he frequently disrobes in front of others, yells at staff, and requires verbal redirection. His MMSE score has fallen to 15. The attending psychiatrist modifies risperidone to 2 mg nightly and adds donepezil, 10 mg each morning, to try to reverse his cognitive decline.

By day 8, Mr. M is more cooperative and his behavior improves. He is transferred back to his board-and-care facility on risperidone and donepezil at the above dosages.

The following month, Mr. M presents to his outpatient psychiatrist with improved cognitive function, but he is still delusional. The psychiatrist stops risperidone and donepezil and resumes olanzapine, 7.5 mg each morning and 10 mg nightly, and chlorpromazine, 50 mg nightly, to try to restore the patient's pre-NMS function.

Mr. M undergoes successful prostate cancer surgery before his 3-month psychiatry follow-up, at which the psychiatrist adds lithium carbonate, 300 mg tid, for residual irritability. Serum lithium levels are normal; bupropion is not restarted.

One year after presentation, Mr. M is minimally delusional but functioning well. No symptoms suggesting NMS recurrence have been reported.

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What caused Mr. M's NMS?

a) a first-generation antipsychotic (FGA)
b) a second-generation antipsychotic (SGA)
c) lithium carbonate
d) bupropion

The authors' observations

Though the precise mechanism is unknown, NMS has been linked with use of FGAs such as chlorpromazine, which can trigger excessive dopamine blockade.[4] Studies increasingly associate SGAs such as olanzapine, risperidone, and aripiprazole with NMS onset.[4-6] Mood stabilizers such as lithium carbonate also have been implicated, especially when used with antipsychotics.[6-9] No association between antibiotics and NMS has been found.

For years, Mr. M has been taking FGAs and concomitant olanzapine and lithium carbonate without developing NMS symptoms until now. Since discharge, he has been free of NMS symptoms despite taking two SGAs (aripiprazole and risperidone) at different times and later resuming chlorpromazine, olanzapine, and lithium carbonate.

Of note, bupropion—the last psychotropic added before NMS onset—has not been restarted. The literature does not link bupropion to NMS, although one case report[10] suggests an association between fluoxetine and NMS after the patient had taken several antipsychotic/antidepressant combinations.

As a dopamine agonist, bupropion should protect against NMS. Case reports,[11,12] however, have described patients who developed NMS after antipsychotics were discontinued, and stopping an antipsychotic essentially mimics bupropion's action by eliminating the dopamine blockade. Additionally, bupropion's norepinephrine modulation could have precipitated NMS by dysregulating the sympathetic nervous system.[13]

Mr. M's board-and-care operator indicated that the patient's tobacco consumption decreased—from about a pack to a half-pack of cigarettes daily—after bupropion was added. Alternatively, the effects of pneumonia could have curtailed Mr. M's smoking. Because nicotine increases metabolism of neuroleptics,[14,15] decreased nicotine consumption might have increased dopamine blockade to the point of causing NMS.

Other possibilities. Mr. M's pneumonia might have caused dehydration, which can also lead to NMS.

Bupropion also reportedly alters metabolism of chlorpromazine and other phenothiazine antipsychotics by inhibiting the cytochrome P-450 2D6 isoenzyme. This pharmacokinetic interaction could have precipitated Mr. M's NMS episode independent of an antipsychotic dosage increase.[16]

Because this case is so complex, pinpointing a specific cause for Mr. M's apparent NMS symptoms is difficult. Be aware that combining psychotropics can lead to NMS. Patients who present with mental status changes, hyperthermia, rigidity, and/or increased creatine kinase while taking psychotropics should be promptly evaluated and managed.

How would you handle this case?

Visit www.**currentpsychiatry**.com to input your answers and compare them with those of your colleagues

TREATING NMS

A review of NMS treatment by Davis et al[17] suggests that you:

- consider NMS in the differential diagnosis of an acutely delirious patient who has used antipsychotics, no matter how long he or she has been taking the medication(s) or how stable the dosage
- check for other signs of NMS—such as

Related resources

- Neuroleptic Malignant Syndrome Information Service. Archive of articles addressing NMS diagnosis and treatment, and listing of psychotropics associated with NMS. www.nmsis.org.

DRUG BRAND NAME

Aripiprazole • Abilify
Benztropine • Cogentin
Bupropion SR • Wellbutrin, Zyban
Ceftazidime • various
Chlorpromazine • Thorazine
Dantrolene • Dantrium
Donepezil • Aricept
Lithium carbonate • various
Lorazepam • Ativan
Olanzapine • Zyprexa
Risperidone • Risperdal

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

rigidity or autonomic instability—during the physical examination.

- consider NMS as a possible cause of dysarthria, diaphoresis, dysphagia, sialorrhea, and myoclonus, although these are less common signs of the disorder
- include CPK levels, chemistry panel, CBC, and liver enzyme assessment in the early evaluation of laboratory results. Consider performing a urine drug screen to check for illicit substance use. Head CT results might also help confirm NMS diagnosis.

Bottom Line

Suspect neuroleptic malignant syndrome (NMS) in an acutely delirious patient who has used antipsychotics. Also find out if the patient is taking another medication that could interact adversely with antipsychotics or with a similar mechanism of action. Temporarily withhold antipsychotics until NMS symptoms abate and other causes of delirium are investigated.

If patient history, physical, and laboratory signs suggest NMS, immediately transfer the patient to a general hospital ICU. Withhold antipsychotics until the NMS episode is resolved, the patient receives aggressive hydration and fluid management, and other causes for delirium are investigated.

If sedation becomes necessary, use benzodiazepines cautiously. Serial CPKs and daily reassessment of clinical degree of rigidity are essential; continued rigidity may indicate use of dopamine agonists and dantrolene.[17]

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