Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

Ms. G thinks nursing home workers want to kill her. An antipsychotic could decrease her paranoia, but she's prone to neuroleptic malignant syndrome. How would you treat her?

When treatment spells trouble

Joshua Kantrowitz, MD
Second-year psychiatry resident

Erica Wojciuk-Jessen, MD
Third-year psychiatry resident

Rajesh R. Tampi, MD, MS
Assistant professor

Department of psychiatry, Yale University School of Medicine, New Haven, CT

HISTORY 'THEY'RE TRYING TO KILL ME'

For the past 7 months Ms. G, age 47, has had worsening paranoid thoughts and sleep disturbances. She sleeps ≤4 hours a night, and her appetite and energy are diminished.

Her mother reports that Ms. G, who lives in an extended-care facility, believes the staff has injected embalming fluid into her body and is plotting to kill her. She says her daughter also has "fits" during which she hears a deafening noise that sounds like a vacuum cleaner, followed by a feeling of being pushed to the ground. Ms. G tells us that someone or something invisible is trying to control her.

Ms. G was diagnosed 2 years ago as having Parkinson's disease and has chronically high liver transaminase enzymes. She also has moderate mental retardation secondary to cerebral palsy. She fears she will be harmed if she stays at the extended-care facility, but we find no evidence that she has been abused or mistreated there.

Three months before presenting to us, Ms. G was hospitalized for 3 days to treat symptoms that suggested neuroleptic malignant syndrome (NMS) but were apparently caused by her inadvertently stopping her antiparkinson agents.

One month later, Ms. G was hospitalized again, this time for acute psychosis. Quetiapine, which she had been taking for antiparkinson medication-induced psychosis, was increased from 100 mg nightly to 75 mg bid, with reportedly good effect.

Shortly afterward, however, Ms. G's paranoia worsened. At the facility, she has called 911 several times to report imagined threats from staff members. After referral from her primary care physician, we evaluate Ms. G and admit her to the adult inpatient psychiatric unit.

At intake, Ms. G is anxious and uncomfortable with notable muscle spasticity and twitching of her arms and legs. Mostly wheelchair-bound, she has long-standing physical abnormalities (shuffling gait; dystonia; drooling; slowed, dysarthric speech) secondary to comorbid Parkinson's and cerebral palsy. She is agitated at first but grows calmer and cooperative.

Mental status examination shows a disorganized, tangential thought process and evidence of paranoid delusions and auditory hallucinations, but she denies

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visual hallucinations. She has poor insight into her illness but is oriented to time, place, and person. She can recall two of three objects after 3 minutes of distraction. Attention and concentration are intact.

Ms. G denies depressed mood, anhedonia, mania, or suicidal or homicidal thoughts. Her mother says no stressors other than the imagined threats to her life have affected her daughter.

The patient's temperature at admission is 98.0ºF, her pulse is 108 beats per minute, and her blood pressure is 150/88 mm Hg. Laboratory workup shows a white blood cell count of 10,100/mm^3 (normal range: 4,000 to 10,000/mm^3), sodium level of 132 mEq/L (normal range: 135 to 145 mEq/L), and aspartate (AST) and alanine (ALT) transaminase levels of 611 U/L and 79 U/L, respectively (normal range for each: 0 to 35 U/L).

Aside from quetiapine, Ms. G also has been taking carbidopa/levodopa, seven 25/100-mg tablets daily, and pramipexole, 3 mg/d, for parkinsonism; citalopram, 20 mg/d, for depression; trazodone, 300 mg nightly, and lorazepam, 0.5 mg nightly, for insomnia; lopressor, 25 mg every 12 hours, for hypertension; and tolterodine, 1 mg bid, for urinary incontinence.

How would you treat Ms. G's psychosis?

- **increase quetiapine dosage**
- **switch to another antipsychotic**
- **try another class of agent**

The authors' observations

Parkinsonism typically responds to dopaminergic treatment. Excess dopamine agonism is believed to contribute to medication-induced psychosis, a common and often disabling complication of Parkinson's disease[1,2] that often necessitates nursing home placement and may increase mortality.[2,3]

Table 1

Factors that increase risk of neuroleptic malignant syndrome*

Abrupt antipsychotic cessation
Ambient heat
Catatonia
Dehydration
Exhaustion
Genetic predisposition
Greater dosage increases
Higher neuroleptic doses, especially with typical and atypical IM agents
Low serum iron
Malnutrition
Mental retardation
Pre-existing EPS or parkinsonism
Previous NMS episode
Psychomotor agitation

* Infection or concurrent organic brain disease are predisposing factors, but their association with NMS is less clear.

EPS: extrapyramidal symptoms

Source: References: 4-7, 14-15.

Paranoia occurs in approximately 8% of patients treated for drug-induced Parkinson's psychosis, and hallucinations (typically visual) may occur in as many as 30%.[2] Quetiapine, 50 to 225 mg/d, is considered a good first-line treatment for psychosis in Parkinson's, although the agent has been tested for this use only in open-label trials.[2,3]

Mental retardation and pre-existing parkinsonism, however, may increase Ms. G's risk for NMS, a rare but potentially fatal reaction to antipsychotics believed to be caused by a sudden D_2 dopamine receptor blockade.[4,5] Signs include

Table 2

Antipsychotic-related NMS risk increases at these dosages

Agent	Dosage (mg/d)
Aripiprazole	>30
Chlorpromazine	>400
Clozapine	318+/-299
Olanzapine	9.7+/-2.3
Quetiapine	412.5+/-317
Risperidone	4.3+/-3.1
Ziprasidone	>120

Source: References 4, 6, and 15.

autonomic instability, extrapyramidal symptoms, hyperpyrexia, and altered mental status.

Of 68 patients with NMS studied by Ananth et al,[4] 13.2% were mentally retarded, and uncontrolled studies[6] have proposed mental retardation as a potential risk factor (*Table 1, page 95*). A 2003 case control study[6] found a higher incidence of NMS among mentally retarded patients than among non-retarded persons, but the difference was not statistically significant. There are no known links between specific causes of mental retardation and NMS.

Even so, Ms. G's psychosis is compromising her already diminished quality of life. We will increase her quetiapine dosage slightly and watch for early signs of NMS, including fever, confusion, and increased muscle rigidity.

TREATMENT MEDICATION CHANGE

Upon admission, quetiapine is increased to 75 mg in the morning and 125 mg at bedtime—still well below the dosage at which quetiapine increases the risk of NMS (*Table 2*). Trazodone is decreased to 100 mg/d because of quetiapine's sedating properties. Citalopram and tolterodine are stopped for fear that either agent would aggravate her psychosis. We continue all other drugs as previously prescribed. Her paranoia begins to subside.

Three days later, Ms. G's is increasingly confused and agitated, and her temperature rises to 101.3ºF. Physical exam shows increased muscle rigidity. She is given lorazepam, 1 mg, and transferred to the emergency room for evaluation.

In the ER, Ms. G's temperature rises to 102.3ºF. Other vital signs include:

- heart rate, 112 to 120 beats per minute
- respiratory rate, 18 to 20 breaths per minute
- oxygen saturation, 98% in room air
- blood pressure, 131/61 mm Hg while seated and 92/58 mm Hg while standing.

We suspect NMS based on her dry mucous membranes, tachycardic but otherwise normal heart, and hand and foot rigidity. Creatine kinase (CK) measured after ER admission is 11,500 U/L, well above the typically elevated levels for a patient with Parkinson's.[8] Also, Ms. G is alert to her name only.

CNS or systemic infection and myocardial infarction are considered less likely because of her reactive pupils, lack of nuchal rigidity, troponin <0.3, and a white blood cell count of 10,200/mm^3. Additionally, CSF shows normal glucose and protein levels, ALT and AST are 217 and 261 U/L, respectively, and chest x-ray shows no acute cardiopulmonary abnormality.

Ms. G is admitted to the medical intensive care unit and given IV fluids. All psychotropic and antiparkinson medications are stopped for 12 hours. Ms. G is then transferred to the general medical service for continued observation and IV hydration.

Six hours later, lorazepam, 0.5 mg every 8 hours, is resumed to control Ms. G's anxiety. Carbidopa/levodopa is resumed at the previous dosage; all other medications remain on hold.

Renal damage is not apparent, but repeat chest x-ray taken 2 days after admission to the ER shows right middle lobe pneumonia, which resolved with antibiotics.

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Six days after entering the medical unit, Ms. G is no longer agitated or paranoid. She is discharged that day and continued on lorazepam, 1 mg every 8 hours as needed to control her anxiety and prevent paranoia, and carbidopa/levidopa 8-$^1/_2$ 25/100-mg tablets daily for her parkinsonism. Trazodone, 100 mg nightly, is continued for 3 days to help her sleep, as is amoxicillin/clavulanate, 500 mg every 8 hours, in case an underlying infection exists. Quetiapine, citalopram, and tolterodine are discontinued; all other medications are resumed as previously prescribed.

Ms. G's NMS symptoms were caused by:
- **increased antipsychotic dosage**
- **pneumonia**
- **another medication**

The authors' observations

Ms. G's NMS symptoms surfaced 3 days after her quetiapine dosage was increased, suggesting that the antipsychotic may have caused this episode.

We ruled out antiparkinson agent withdrawal malignant syndrome—usually caused by abrupt cessation of Parkinson's medications. Ms. G's carbidopa/levodopa had not been adjusted before the symptoms emerged, and she did not worsen after the agent was stopped temporarily. Her brief pneumonia episode, however, could have caused symptoms that mimicked this withdrawal syndrome.

Antiparkinson agent withdrawal malignant syndrome symptoms resemble those of NMS.[9,10] Worsening parkinsonism, dehydration, and infection increase the risk.[10] Some research suggests that leukocytosis or elevated inflammation-related cytokines may accelerate withdrawal syndrome.[10]

Following Ms. G's NMS episode, how would you treat recurrent delusional paranoia?
- **restart quetiapine**
- **try another antipsychotic**
- **consider alternate therapy**

The authors' observations

Ms. G's case illustrates the difficulty of treating psychosis in a patient at risk for NMS.

Of the 68 patients in the Ananth et al study with atypical antipsychotic-induced NMS, 11 were rechallenged after an NMS episode with the same agent and 8 were switched to another atypical. NMS recurred in 4 of these 19 patients.[4]

Ms. G was stable on lorazepam at discharge, but we would consider rechallenging with quetiapine or another antipsychotic if necessary. NMS recurs in 30% to 50%[11] of patients after antipsychotic rechallenge, but waiting 2 weeks to resume antipsychotic therapy appears to reduce this risk.[12] Benzodiazepines and electroconvulsive therapy are acceptable—though unproven—second-line therapies if antipsychotic rechallenge is deemed too risky,[11,13] such as in some patients with a previous severe NMS episode; evidence of stroke,

Bottom Line

When treating psychosis in patients at risk for NMS, watch closely for confusion, fever, and other signs that signal this potentially fatal reaction to neuroleptics. Waiting 2 weeks after the NMS episode before restarting the allegedly "offending" antipsychotic may reduce the risk of NMS recurrence.

Parkinson's or other neurodegenerative disease; or multiple acute medical problems.

CONTINUED TREATMENT A RELAPSE

Three months later, Ms. G is readmitted to the neurology service for 3 weeks after being diagnosed with elevated CK, possibly caused by NMS or rhabdomyolysis secondary to persistent dyskinesia. We believe an inadvertent decrease in her carbidopa/levodopa caused the episode, as she had taken no neuroleptics between hospitalizations.

Ms. G is discharged on quetiapine, 25 mg nightly, along with her other medications. Her current psychiatric and neurologic status is unknown.

The authors' observations

Detecting NMS symptoms early is critical to preventing mortality. Although NMS risk with atypical and typical antipsychotics is similar,[4] fewer deaths from NMS have been reported after use of atypicals (3 deaths among 68 cases) than typical neuroleptics (30% mortality rate in the 1960s and 70s, and 10% mortality from 1980-87).[14] Earlier recognition and treatment may be decreasing NMS-related mortality.[4]

Consider NMS in the differential diagnosis when the patient's mental status changes. Watch for risk factors, warning signs, and symptoms in patients taking neuroleptics.

Related resources

- Emedicine: Neuroleptic malignant syndrome. www.emedicine.com/med/topic2614.htm.
- Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. *Neurol Clin* 2004;22:389-411.
- Susman VL. Clinical management of neuroleptic malignant syndrome. *Psychiatr Q* 2001;72:325-36.

DRUG BRAND NAMES

Amoxicillin/clavulanate • Augmentin
Aripiprazole • Abilify
Carbidopa/levodopa • Sinemet
Chlorpromazine • Thorazine
Citalopram • Celexa
Clozapine • Clozaril
Lopressor • Toprol
Lorazepam • Ativan
Olanzapine • Zyprexa
Pramipexole • Mirapex
Quetiapine • Seroquel
Risperidone • Risperdal
Tolterodine • Detrol
Trazodone • Desyrel
Ziprasidone • Geodon

DISCLOSURE

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

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