Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

After 30 years, Mr. S' catatonic schizophrenia finally responds to medication, but the drug causes a precipitous WBC decrease. The challenge: find a tolerable yet effective regimen.

When clozapine is not an option

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HISTORY 'LEAVING TOWN'

Mr. S, age 58, escaped repeatedly from his group home over 4 weeks. During one episode, he removed mail from neighbors' mailboxes and tried to direct midday traffic. He would disappear for a few hours, sometimes overnight, before returning or being brought back by police.

The patient—who has had schizophrenia with catatonic features for 30 years—offered assorted explanations for escaping, most of them based on delusional beliefs, such as "I'm leaving town to get married" or "I'm late for engineering class."

Since his last escape 3 weeks ago, Mr. S has remained in the group home without incident but has not been reporting for his usual outpatient psychiatric care. One day, he finally presents to us at the group home sponsor's urging.

On evaluation, Mr. S shows stereotyped speech, staring, posturing, speech-prompt mutism, and odd mannerisms such as saluting. He has not been bathing or sleeping and smiles inappropriately. He speaks only when spoken to and answers with short phrases punctuated with "By the grace of the good Lord."

The authors' observations

DSM-IV-TR requires at least two features to diagnose catatonic schizophrenia:

- peculiar voluntary movements
- extreme negativism
- excessive motor activity
- echolalia or echopraxia
- motoric immobility.[1]

Mr. S has the first three features.

Catatonia is common among the chronic mentally ill,[2] yet it often goes undiagnosed.[3] As a form of psychosis, catatonia might lead to greater functional impairment if not treated.

Table

Treatments for catatonia: risks and benefits

Medication	Use	Rationale	Benefits	Risks
First-generation antipsychotics (FGAs)	Often used for schizophrenia	Control positive symptoms	Well-established Less expensive than other medications	Catatonia might be difficult to distinguish from NMS
Second-generation antipsychotics (SGAs)	Beneficial in catatonia	Less likely than FGAs to worsen catatonia because of low D2 blockade	Some studies suggest greater efficacy than with FGAs	Metabolic syndrome, agranulocytosis with clozapine
Benzodiazepines	Lorazepam helpful in acute catatonia	Can be added to any antipsychotic	Safe, first-line treatment for catatonia	Respiratory compromise, incoordination, sedation, potential for abuse
Electroconvulsive therapy	Beneficial in malignant catatonia	Effective in catatonia, NMS	Useful for treatment-refractory catatonia Rapid onset of action	Concerns with anesthesia, informed consent, availability

NMS: Neuroleptic malignant syndrome

TREATMENT TIME TO TRY CLOZAPINE?

Over 10 years, numerous antipsychotic regimens plus adjunctive valproic acid, 500 mg tid, or lorazepam, up to 2 mg tid, have not lessened Mr. S' psychosis and impulsivity. We start clozapine, 400 mg/d, and order twice-monthly blood tests to check for clozapine-induced agranulocytosis.

After nearly 6 months, some catatonic features improve gradually based on clinical interview. Serum clozapine is 363 ng/mL.

How would you have treated Mr. S' delusions and impulsive behavior at this stage?

a) try clozapine

b) consider electroconvulsive therapy (ECT)

c) increase adjunctive lorazepam

d) try another option

The authors' observations

Second-generation antipsychotics (SGAs) are favored over first-generation antipsychotics to treat schizophrenia with catatonic features (*Table*),[4,5] but no drug in either class has worked for Mr. S.

ECT can alleviate catatonic schizophrenia,[4,6] but this option often is not available because the clinician fears a negative outcome would prompt legal action, or the guardian or next of kin do not consent to the procedure.[3] We considered referring Mr. S to an ECT provider, but he has no legal guardian to provide consent. The group home sponsor also objected to ECT because Mr. S would have been sent out of town for treatment.

Catatonia patients who are immobile, physically compromised, and refuse food and drink typically are considered ECT candidates. Mr. S eats and drinks regularly and is physically able.

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How would you handle this case?

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Lorazepam can produce rapid response, but it can be addictive.[2] Also, an adjunctive 2 mg/d dosage showed no effect.

Clozapine monotherapy has shown effectiveness in catatonic schizophrenia[7] and might be an option after other antipsychotics have failed.

COMPLICATION AGRANULOCYTOSIS, THEN NMS

Six months after starting clozapine, Mr. S starts having diaphoresis and night sweats, suggesting neutropenia. Blood testing shows a white blood cell count (WBC) of 3.6/μL, down from 4.6/μL 2 weeks before (normal range, 4.6 to 11/μL).

One week later, Mr. S' WBC is 1.6/μL with a 46% relative neutrophil value (normal range, 50% to 70%) and an absolute neutrophil count of 736 (normal range, 2,500 to 7,000).

We diagnose agranulocytosis and stop clozapine, but Mr. S' WBC continues to fall over 2 weeks to 0.8/μL with a 16% relative and 128 absolute neutrophil count. After 1 more week, his WBC increases to 2.6/μL and returns to normal 1 week later—4 weeks after stopping clozapine

We then target Mr. S' catatonia with intramuscular haloperidol, 100 mg/d for 4 weeks, and ziprasidone, 80 mg bid with food. He tolerates this combination but gradually develops tremor and rigidity. Six weeks later, we add levodopa/carbidopa, 25/250 mg bid for his movement problems.

Two weeks later, Mr. S is sweating profusely, disoriented, rigid, and febrile (104.6°F). We diagnose neuroleptic malignant syndrome (NMS), stop both antipsychotics, and admit him for treatment. We start lorazepam, 1 mg tid for catatonia; bromocriptine, 250 mg bid for rigidity; and continue levodopa/carbidopa at the same dosage. We also add dantrolene, 25 mg tid for 5 days for fever and rigidity, and provide a cooling blanket for hyperthermia.

Mr. S' fever, autonomic changes, and diaphoresis diminish within 3 days. Rigidity and mental status improve gradually over 2 weeks. We discharge him after 10 days.

What caused Mr. S' NMS?

a) haloperidol

b) catatonia

c) ziprasidone

The author's observations

Catatonia is a recognized risk factor for NMS. White and Robins[8] described 17 patients with a catatonic syndrome that developed into NMS within 5 to 96 hours of starting a neuroleptic. Sachdev developed an NMS rating scale that includes catatonic symptoms.[9]

Northoff,[10] however, associates NMS with D2 receptor blockage in the basal ganglia and relates catatonia to a frontocortical gamma-aminobutyric acid (GABA) dysfunction. Based on this theory, haloperidol—which offers a higher D2 blockade than do SGAs such as ziprasidone—might have contributed to Mr. S' NMS.

Some evidence suggests that lorazepam—which works on gamma-aminobutyric acid ionotropic type A (GABAA) receptors—helps treat catatonia in NMS and improves rigidity, hyperthermia, and autonomic signs.[11]

TREATMENT WHICH AGENTS WILL WORK?

Three weeks after his discharge, we restart ziprasidone, 40 mg bid for Mr. S' catatonic schizophrenia. He remains free of NMS symptoms but still has mannerisms (posturing, staring, immobility, stereotypic scratching on his face).

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Over 1 year, Mr. S is hospitalized repeatedly because of persistent impulsivity and delusions. He has failed numerous antipsychotic regimens lasting 1 month or longer, including olanzapine, up to 30 mg/d; quetiapine, 300 mg tid; and risperidone, 2 mg tid. Adding a first-generation antipsychotic either does not help (as with perphenazine, 12 mg/d) or diminishes his memory (as with chlorpromazine, 250 mg/d). The anticholinergic benztropine, 2 mg bid, also is ineffective.

Combination quetiapine, 300 mg/d, and the antiviral amantadine, 100 mg tid, improve Mr. S' stereotypy at first, but his delusions intensify within 1 week. His Bush-Francis Catatonia Rating Scale scores range from 9 (indicating moderate catatonia) to 16 (persistent catatonic features).[12]

Catatonia's response to medication might differ compared with other forms of schizophrenia

Which medications could help Mr. S?

a) another antipsychotic
b) antipsychotic with lorazepam
c) anticonvulsants
d) another class of medication

The authors' observations

Catatonic schizophrenia's pathophysiology and response to medication might differ compared with other schizophrenia forms.[13] Dopamine D2 hypoactivity, glutamate N-methyl-D-aspartate (NMDA) hyperactivity, or GABAA hypoactivity are believed to cause catatonia.[3,6,7] GABA agonists, anticonvulsants, dopamine agonists, SGAs, and NMDA antagonists target these pathophysiologies, but patients with a catatonia subtype often respond to only one type of medication.

Lorazepam exerts an anticatatonic effect by binding to GABAA receptors and increasing GABA activity. Lorazepam can help some patients with schizophrenia but has not shown benefit when added to an antipsychotic for chronic catatonia.[6,14]

SGAs can provide marked improvement in patients with catatonic schizophrenia.[5]

Salokangas et al[15] note that "atypicals" pass more dopamine to the D2 receptor when dopamine is low in the basal ganglia. This suggests that SGAs with low D2 binding—such as clozapine, olanzapine, and quetiapine—are more beneficial than other SGAs for catatonia. Serotonin binding or other mechanisms might add to these drugs' anticatatonic effect.[7]

Anticonvulsants. Adjunctive anticonvulsant therapy might alleviate catatonia by increasing GABA activity or by causing a modest antiglutaminergic effect, as reported with carbamazepine or valproic acid.[16] Anticholinergics also might help treat neuroleptic-induced catatonia.[17]

Amantadine—FDA-approved to treat Parkinson's disease and extrapyramidal disease—can alleviate catatonia by blocking hyperglutamatergic excitotoxicity in neurons, thus blocking NMDA receptors.[18] As with Mr. S, however, amantadine can worsen psychosis by increasing dopamine release.

Memantine—an NMDA receptor antagonist indicated for moderate to severe Alzheimer's disease—also blocks hyperglutamatergic excitotoxicity in neurons. The medication has shown effectiveness for treating catatonic schizophrenia in case reports,[19-21] but 3 patients have reported memantine-induced psychosis and seizures.[21]

Some might argue that Mr. S' delusions are predominant and more compelling than his catatonia, but these did not hamper his ability to live in a group home. His catatonia-related negativism, impulsivity, and inability to cooperate are what led to frequent hospitalization.

FOLLOW-UP TREATMENT CHANGE

We stop amantadine, add memantine, 10 mg bid, and titrate quetiapine over 2 weeks to 900 mg/d. Mr. S' catatonia improves but some delusions

persist. We add olanzapine, 7.5 mg bid, and within 2 weeks Mr. S is less delusional and more cooperative.

We discharge Mr. S on the above medications, plus:

- lorazepam, 1 mg each morning and 2 mg nightly, which he has been taking for catatonia for about 1 year
- trazodone, 150 mg bid, which we added 6 months ago to help him sleep and reduce psychomotor excitement
- ranitidine, 150 mg bid, for gastroesophageal reflux disorder
- and levothyroxine, 0.5 mg/d, for comobrid hypothyroidism. His thyroid-stimulating hormone level is normal.

At outpatient follow-up 3 weeks later, Mr. S' Bush-Francis Catatonia Rating Scale score is 5, suggesting reduced catatonic features; subcategory scores for primary catatonia symptoms (immobility, staring, and mundane posturing) are low. He offers some equivocal automatic obedience without mitgehen, mitmachen, gegenhalten, grasp reflex, catalepsy, or waxy flexibility.[12]

We see Mr. S monthly. He is still impulsive at times, occasionally collecting his neighbors' newspapers and mail despite instructions from group home staff not to do so. Yet his sponsors say Mr. S is "like a new person." He talks spontaneously, interacts, and is cooperative. He has not been hospitalized for more than 1 year.

Bottom Line

In treatment-refractory catatonic schizophrenia, dopamine agonists, anticonvulsants, GABA agonists, NMDA agonists, and some second-generation antipsychotics can help patients who cannot tolerate clozapine. Patients respond differently to each drug, so finding the right regimen may involve trial-and-error.

The authors' observations

Mr. S responded favorably to clozapine but cannot tolerate it. With a combination of two other SGAs, a patient might gain the benefits of clozapine without the need for frequent blood draws or the risk of agranulocytosis, other side effects, or interactions between clozapine and other drugs. Adding memantine was necessary to improve the catatonic features that prevented his return to the group home.

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Related resources

- World Federation of Societies of Biological Psychiatry. www.wfsbp.com.
- Neuroleptic Malignant Syndrome Information Service. www.nmsis.org.
- Mann SC, Caroff SN, Keck PE Jr, Lazarus A. *Neuroleptic malignant syndrome and related conditions, 2nd ed.* Arlington, VA: American Psychiatric Press; 2003:1-44.
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DRUG BRAND NAMES

Amantadine • Symmetrel
Benztropine • Cogentin
Bromocriptine • Parlodel
Carbamazepine • Equetro, others
Chlorpromazine • Thorazine
Clozapine • Clozaril
Dantrolene • Dantrium
Haloperidol • Haldol
Levodopa/carbidopa • Sinemet
Levothyroxine • Synthroid
Lorazepam • Ativan
Memantine • Namenda
Olanzapine • Zyprexa
Perphenazine • Trilafon
Quetiapine • Seroquel
Ranitidine • Zantac
Risperidone • Risperdal
Trazodone • Desyrel
Valproic acid • Depakene
Ziprasidone • Geodon

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