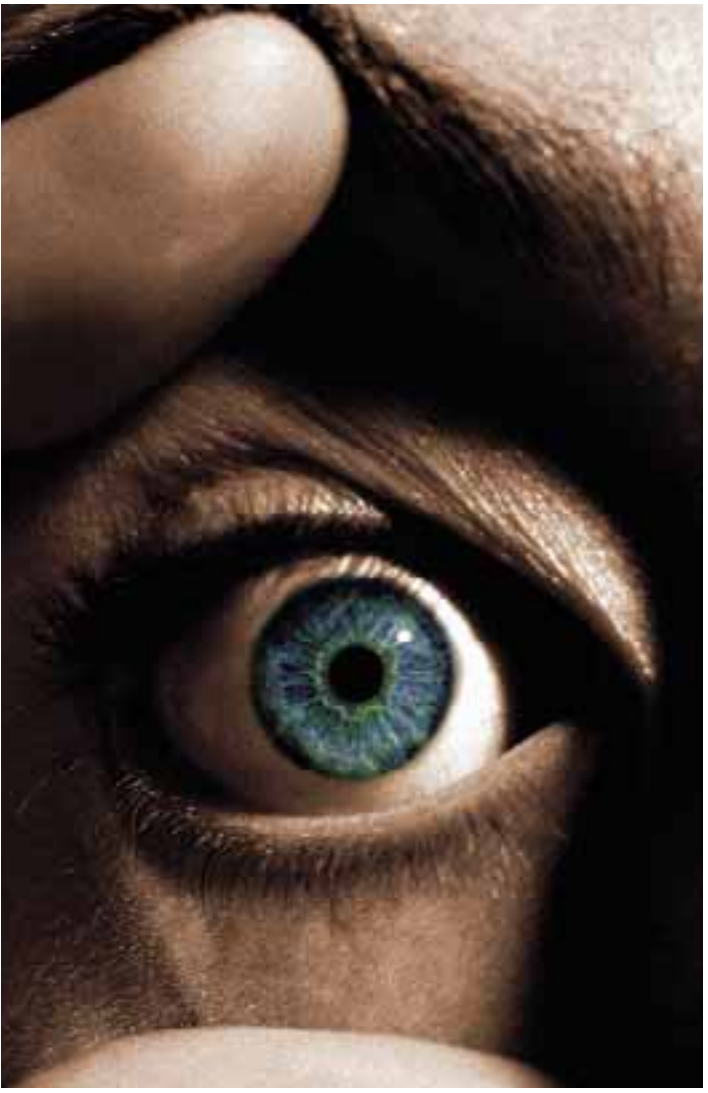
Current Psychiatry

Treating persistent catatonia when benzodiazepines fail

Neural circuit changes help explain syndrome's signs, suggest potential therapies



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Brendan T. Carroll, MD
Associate professor of psychiatry (volunteer)
University of Cincinnati, Cincinnati, OH

Christopher Thomas, PharmD
Clinical pharmacy specialist in psychiatry
VA Medical Center, Chillicothe, OH

Kameshwari Jayanti, MD
Psychiatry service, Mental health care line
VA Medical Center, Chillicothe, OH

John M. Hawkins, MD
Assistant professor of psychiatry (volunteer)
University of Cincinnati, Cincinnati, OH

Carrie Burbage, BS
Physician assistant student
Marietta College, Marietta, OH

Many catatonia cases respond to benzodiazepines—especially lorazepam—but up to 30% do not. Electroconvulsive therapy (ECT) can be effective, but what's the next step when ECT is unavailable or inappropriate for your patient?

To help you solve this dilemma, we describe our diagnosis and treatment decisions for a patient we call Mr. C. We explain how our process was guided by recent understandings of an abnormal neural circuit that appears to cause catatonia's complex motor and behavioral symptoms.

This article describes that neurologic pathology and answers common questions about the clinical workup and treatment of catatonia.

CASE: TROUBLE IN TV LAND

Mr. C, age 69, caused a disturbance at a local TV station, demanding that they broadcast a manuscript he had written. Police took him to a local hospital, where he was stabilized and then transferred to a neuropsychiatric hospital for evaluation.

The psychiatric interview revealed that he had developed insomnia, excessive activity, and delusional thinking 2 weeks before admission. His medical history included coronary artery disease (CAD), hypertension, and hypothyroidism. Medications included thyroid hormone replacement therapy, furosemide, potassium, ranitidine, simvastatin, metoprolol, and lisinopril. CAD treatment included stent placement and nitroglycerin as needed.

He had been hospitalized in his 30s and treated with ECT for what he called "bad thoughts." He said he improved after 1 month and had no subsequent psychiatric history. He denied drug or alcohol abuse.

Shortly after admission, he refused to eat or drink and after 1 week became dehydrated. He also showed mutism, immobility, and stupor. He was transferred to the medical service for IV rehydration.

MANY SCENARIOS AND SIGNS

Mr. C's symptoms suggest possible catatonia, a neuropsychiatric syndrome of motor dysregulation found in up to 10% of acutely ill psychiatric inpatients.[1,2] A movement disorder,[1,2] catatonia occurs with general medical conditions and psychiatric disorders *(Table 1)*.

Pathophysiology. Catatonic signs develop when aberrant signals from neurochemical abnormalities trigger a neural circuit that affects the medial gyrus of the orbital frontal lobe, the lateral gyrus, caudate nucleus, globus pallidus, and thalamus *(Box, page 58)*.[3-5]

Presentation. A focused exam is required because patients with catatonia often do not provide a comprehensive or reliable history.[2] They show mutism, characteristic postures, rigidity, aberrant speech, negativism, and stereotyped behaviors.[1,2] They may present in an excited or retarded state:

- Excited patients may injure themselves or others and develop hyperthermia, tachycardia, and elevated blood pressure from excessive motor activity.
- Patients in a retarded state may present with bradykinesia and poor self-care. They may be unresponsive to external stimuli, develop catatonic stupor, and refuse to eat or drink.

Mr. C's earlier insomnia, excessive activity, and delusional thinking (such as the TV station incident) may have signaled an excited catatonia. On admission to the medical service, however, he presented in a retarded state.

Signs. Part of the challenge with detecting catatonia's signs is that there are so many; some rating scales list more than 20. Not all signs need to be present to make the diagnosis, however, and if you find one, others usually turn up in the examination.

A mnemonic from the Bush-Francis Catatonia Screening Instrument *(Table 2, page 59)* represents diagnostic signs in patients with the excited or

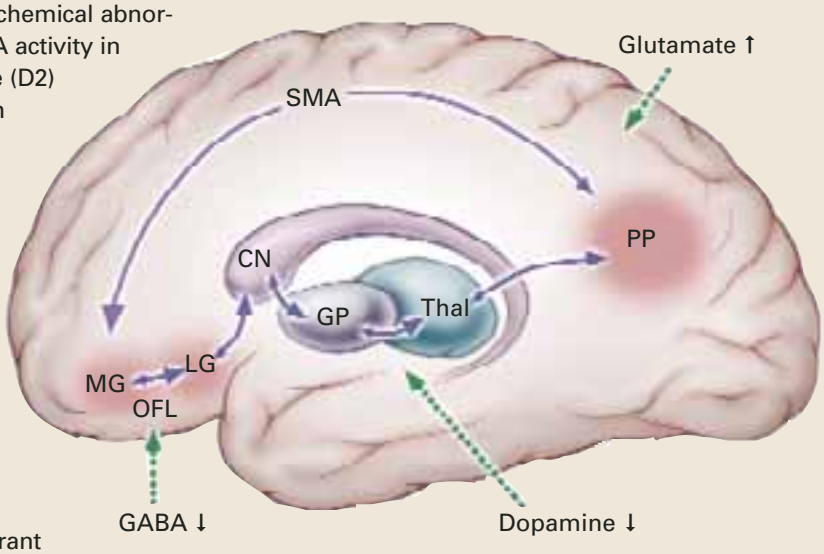
Table 1
Common diagnoses of patients with catatonia

Psychiatric	• Schizophrenia • Mood disorder (depression, bipolar disorder [manic, mixed, depressed]) • Other psychoses • Personality or conversion (somatoform) disorders • Developmental disorders (autism)
Organic	• Due to a general medical condition • Drug-induced • Idiopathic

Box

Neural loop may explain catatonia's symptoms and treatment response

Catatonia is caused by neurochemical abnormalities including low GABA activity in the frontal cortex, low dopamine (D2) activity in the basal ganglia, high glutamate—N-methyl-D-aspartate (NMDA)—activity in the parietal cortex, or a combination of these.[3-5] Catatonic signs occur when these neurochemical changes cause aberrant signals and trigger a neural circuit affecting the medial gyrus of the orbital frontal lobe, the lateral gyrus, caudate nucleus, globus pallidus, and thalamus (Figure).



MG—medial gyrus
OFL—orbital frontal lobe
LG —lateral gyrus
CN—caudate nucleus
GP—globus pallidus
Thal—thalamus
PP—posterior parietal lobe
SMA—supplemental motor area

Posturing occurs when the aberrant signal reaches the posterior parietal lobe. Patients' bizarre and mundane postures in catatonia are maintained by "anosognosia of position." For example, an individual does not know the position of rest for his arm, and it remains in an unusual position as if at rest.[3]

The PP goes on to influence the supplemental motor area (SMA), causing bradykinesia, rigidity, and other motor phenomena that catatonia shares with Parkinson's disease. The SMA feeds back to the medial orbital gyrus, completing the neural circuit.[3]

Regions such as the anterior cingulate area (ACA) and amygdala (AMG) — also may be recruited into the expanded circuit. ACA recruitment may cause akinetic mutism, and fear is a symptom of AMG recruitment. If the anterior hypothalamus is affected, malignant catatonia or neuroleptic malignant syndrome may occur.[3,5]

This neural loop demonstrates an integrated model of psychosis. It may help explain why catatonia responds to treatment with lorazepam, ECT, and other agents such as antipsychotics and NMDA antagonists.

Illustration for CURRENT PSYCHIATRY by Marcia Hartsock, CMI

retarded forms.[2] We recommend that you review an authoritative text (see *Related resources*, *page 64*) to understand catatonia's psychopathology.[2]

CASE CONTINUED: MAKING THE DIAGNOSIS

In the medical unit, Mr. C was found to be in a catatonic stupor, with immobility, mutism (monosyllabic speech), catalepsy, intermittent waxy flexibility, withdrawal (refusal to eat and drink), automatic obedience, and mitgehen (exaggerated movements in response to light finger pressure, despite instructions to stay still). ECT work-up was started, along with a trial of lorazepam, 1 mg tid.

Laboratory studies revealed high BUN/creatinine (80/2.0) that returned to normal range (BUN 7 to 21 mg/dL; creatinine 0.5 to 1.2 mg/dL) after 3 days of

hydration. Because of Mr. C's earlier excited symptoms and delusional thinking, we considered a diagnosis of bipolar disorder with catatonia. However, his symptoms did not improve with a trial of valproic acid (serum level 64 mcg/mL).

Head CT showed generalized atrophy and EEG showed delta slowing. Single-photo emission computer tomography (SPECT) showed areas of decreased perfusion in the cortex, with no perfusion in the left posterior parietal area (PP).

Mental status exam found Mr. C disoriented with poor short-term memory and unable to complete the Mini Mental State Examination (MMSE). His Bush-Francis Catatonia Rating Scale score was 28 and included many catatonic signs that would not be seen a patient with simple dehydration.

The workup supported a diagnosis of catatonia due to general medical condition (vascular dementia) and ruled out schizophrenia with catatonic features, bipolar disorder, or major depression with catatonia.

EVALUATION AND DIAGNOSIS

Medical causes. A careful history and thorough physical examination are essential for making an accurate diagnosis and ruling out medical conditions that could present with or mimic catatonia *(Table 3, page 60)*. Medications that can induce catatonia include antipsychotics, corticosteroids, and disulfiram at therapeutic doses. Drug abuse (such as with phencyclidine), use of the general anesthetic ketamine, and benzodiazepine withdrawal may also lead to catatonia.

Head CT or MRI is indicated for patients being considered for ECT or for localizing neurologic findings. EEG can be useful when patients present with features of seizure activity—such as tongue biting, incontinence, or stupor—or with catatonia as a manifestation of delirium or dementia.

A history of head injury or neurologic disease warrants further neurologic investigation. Also consider a neurology consult when the patient has prolonged stupor or does not respond to initial drug therapy.

Table 2

WIRED `N MIRED: Mnemonic for detecting catatonia

Waxy flexibility/catalepsy
Immobility/stupor
Refusal to eat or drink
Excitement
Deadpan staring
Negativism/negative symptoms
Mutism
Impulsivity
Rigidity
Echolalia/echopraxia
Direct observation

Psychiatric causes. The clinical setting may suggest the most likely primary psychiatric disorders to consider, such as:

- bipolar or major depression in acute inpatient psychiatric units
- autism and pervasive developmental disorders (PDD) in pediatric or PDD units
- catatonic schizophrenia in chronic psychotic patients
- somatoform or factitious disorders in forensic settings.

These generalizations are not clinically exclusive, of course, but may provide a starting point for the treatment team confronted with limited history and exam information.

Initial treatment. Catatonia related to medical and psychiatric causes has been shown to respond to lorazepam and to ECT.[6,7] Lorazepam is preferred because of its specificity for the GABAa receptor and ease of administration (oral, IM, or IV). Other agents that act on GABA—including amobarbital and zolpidem—have also been used. Catatonia's hallmark features such as mutism

Table 3
Catatonia workup: Recommended lab tests

Test	Recommendation
Complete blood count with WBC differential	Look for leukocytosis
Serum chemistries	Look for electrolyte imbalances
Serum iron	May be low in NMS
Serum creatine kinase	If NMS is suspected
Brain MRI or CT	If structural lesion is suspected
Electroencephalography	If seizure disorder or brain abnormality is suspected
Lumbar puncture	If encephalitis or meningitis is suspected

NMS: neuroleptic malignant syndrome

and immobility have been shown to respond to lorazepam.[8,9]

ECT is a first-line treatment for catatonia with life-threatening conditions and should be considered for refractory cases.

Lorazepam. The starting dosage is usually 1 mg tid for healthy adults; 0.5 mg tid can be used for children and the elderly. Observe the patient for improvement in catatonic signs after the first dose and before giving the second. Dosages of up to 16 mg/d have been used.

In many cases, lorazepam can be tapered off after adequate treatment of the primary psychiatric condition. In severe cases, however—such as when patients refuse to eat or drink—lorazepam may be continued for as long as 1 year. Weigh the risk of benzodiazepine tolerance, dependence, and misuse versus the possibility of relapse and rehospitalization.

Medical catatonias and neuroleptic malignant syndrome (NMS) have responded favorably to ECT.[8] Addressing the medical cause itself usually does not resolve catatonia, with the possible exception of seizure-induced ("ictal") catatonia, which may respond to anticonvulsants and lorazepam.[6,7]

ECT. An ECT workup can begin as soon as a patient presents with catatonia. If lorazepam produces no response within 24 hours, consider ECT.

CASE CONTINUED: PERSISTENT SYMPTOMS

After three 1-mg doses of lorazepam, Mr. C became more alert and oriented but his catatonia symptoms persisted, as indicated by a Bush-Francis score of 23, significant grasp reflex, and gegenhalten (automatic rather than willful resistance to passive limb movement in proportion to the strength of the stimulus). An attempt to gradually increase lorazepam to 2 mg tid produced delirium. He remained confused even when lorazepam was reduced to 0.5 mg tid, so the drug was discontinued.

Mr. C's neurologist added amantadine, 100 mg tid, and carbidopa/levodopa, 10/100 mg tid, to treat his parkinsonian rigidity.

WHAT NEXT? OTHER OPTIONS

Antipsychotics have been investigated as a possible treatment for catatonia. The literature suggests that conventional antipsychotics may cause catatonia and atypical antipsychotics may improve it. Conventional antipsychotics are best avoided in catatonia because they:

- appear less effective than other treatments in resolving catatonic symptoms[8,10]
- are associated with catatonic-like side effects, such as rigidity, akinesia, and staring[10]
- appear to increase NMS risk in patients with catatonic symptoms.[11,12]

Atypicals appear more effective in treating catatonia and less likely to cause NMS. Case reports[13,14] indicate many of these agents can be effective and well tolerated in treating catatonic symptoms, although this was not the case for Mr. C.

continued on page 63

continued from page 60

Anticonvulsants such as valproate[15] and carbamazepine, 600 to 1200 mg/d,[16] may take longer to work than lorazepam but may be options for patients who do not respond to benzodiazepines.[8,9]

Amantadine, an N-methyl-D-aspartate (NMDA) antagonist, has been used with some success for catatonia that does not unrespond to lorazepam.[17] However, amantidine's dopamine agonist activity could worsen underlying psychosis.

Memantine—another NMDA antagonist—differs from amantadine despite having a similar chemical structure. Memantine is a noncompetitive antagonist at the NMDA receptor, without affinity for dopamine, norepinephrine, serotonin, or muscarinic receptors.[18]

Although no published data support using memantine in patients with catatonia, it might be considered for those who are not candidates for lorazepam or ECT. For instance, a double-blind, placebo-controlled study found that lorazepam was not effective for catatonic schizophrenia.[19] We have found memantine to help in some patients with catatonic schizophrenia.

CASE CONTINUED: TRIAL OF MEMANTINE

Mr. C remained in a catatonic stupor, but we decided against ECT because he resumed eating and drinking and was not medically at risk. Quetiapine, 100 to 300 mg/d, was tried to address his dementia symptoms, confusion, and poor mentation. This trial was discontinued after Mr. C fell and was readmitted to the medical unit. We then added memantine, 5 mg bid.

In the first week after beginning memantine, Mr. C's MMSE score was 21, consistent with vascular dementia, but he remained immobile and staring. Motor signs also persisted, including automatic obedience, ambitendency, and a grasp reflex.

The next week, we increased memantine to 10 mg bid. Mr. C was oriented to person, place, and time, and his affect was blunted. His MMSE score increased to 25, showing improved cognition and memory. His Bush-Francis scale score was 6, showing reduced catatonic signs, with remaining mild immobility, bradykinesia, speech-prompt mutism, staring, and grasp reflex.

He maintained this improvement on carbidopa/levodopa, 10/100 tid; amantadine, 100 mg tid; and memantine, 10 mg bid, and was discharged from the nursing home unit.

IMPROVEMENT WITH MEMANTINE

Memantine may reduce excess glutamate at the NMDA receptor in the parietal-SMA-frontal cortical circuit. It may help to increase GABA and dopamine, which are deficient in catatonia. Our patient with vascular dementia had a severe ischemic deficit in the posterior parietal area, as seen on SPECT.

Amantadine, another NMDA receptor antagonist, acts on dopamine neurons and may have anticholinergic-like side effects, whereas memantine does not. Although both drugs share antagonism at the NMDA glutamate receptor, noncompetitive binding is weak for amantadine and moderate for memantine. Memantine has some serotonin (5-HT3) antagonism, but neither agent has direct GABA activity.

Memantine can improve function in vascular dementia.[20] Thus, Mr. C's improvement may

Bottom Line

Catatonia is a complex syndrome that occurs with primary psychiatric disorders or medical conditions. About one-third of patients do not respond to lorazepam, and ECT is not always practical or desired. Agents such as memantine that act on the glutamatergic system may offer additional treatment options.

Related resources

- Fink M, Taylor MA. *Catatonia: a clinician's guide to diagnosis and treatment*. Cambridge, UK: Cambridge University Press, 2003.
- Caroff SN, Mann SC, Francis A, Fricchione GE. *Catatonia: from psychopathology to neurobiology*. Washington, DC: American Psychiatric Publishing, 2004.
- Mann SC, Caroff SN, Keck PE Jr, Lazarus A. *Neuroleptic malignant syndrome and related conditions (2nd ed)*. Washington, DC: American Psychiatric Publishing, 2003.
- Neuroleptic Malignant Syndrome Information Service. www.NMSIS.org

DRUG BRAND NAMES

Amantadine • Symmetrel
Amobarbital • Amytal sodium
Carbamazepine • Carbatrol, Equetro
Carbidopa/levodopa • Sinemet
Disulfiram • Antabuse
Divalproex • Depakote
Furosemide • Lasix
Lisinopril • Prinivil, Zestril
Lorazepam • Ativan
Memantine • Namenda
Metoprolol • Lopressor
Ranitidine • Zantac
Simvastatin • Zocor
Valproic acid • Depakene
Zolpidem • Ambien

DISCLOSURE

Dr. Carroll and Dr. Hawkins are speakers for Forest Laboratories. The other authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

ACKNOWLEDGMENT

The authors thank Dr. Niraj Ahuja, consultant psychiatrist and honorary clinical lecturer (psychiatry), Newcastle, North Tyneside and Northumberland Mental Health Trust, UK, for assistance with the figure.

have been caused by the drug's effect on his vascular dementia, the primary neuropsychiatric illness. However, his catatonic signs improved without antipsychotics, cholinesterase inhibitors, benzodiazepines, or ECT. No anticoagulation treatment or cerebral perfusion procedures account for his improved mental status.

CASE CONCLUSION

Mr. C went to live with his son's family. Although he has problems with calculation, he shows good self-care. When asked why he did not respond during his catatonic stupor, Mr. C stated that he believed the physician was an Internal Revenue Service agent asking him about serious tax problems. Upon reflection, he said he no longer believes this.

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