Between a rock and a hard place

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How would you handle this case?

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While hospitalized for cardiogenic shock, Mr. B, age 75, alternates between appearing delirious and catatonic. Until now, his schizophrenia had been stable. How can you best help him?

CASE Irritable and short of breath

Mr. B, age 75, who lives alone, is brought to the emergency department (ED) for evaluation of shortness of breath. Mr. B is normally highly independent, and is able to drive, manage his own finances, attend to activities of daily living, and participate in social functions at church. On the day before he was taken to the ED, his home nurse had come to his home to dispense medications and found Mr. B was irritable, verbally rude, and repeatedly scratching the right side of his head. The nurse was unsure if Mr. B had taken his medications over the weekend. She called for emergency services, but Mr. B refused to go to the ED, and he was able to decline care because he was not in an acute medical emergency (95% oxygen on pulse oximetry).

The next day, when Mr. B's nurse returned to his home, she found him to be tachypneic and verbigerating the phrase "I don't know." She contacted emergency services again, and Mr. B was taken to the ED.

In the ED, Mr. B has tachycardia, tachypnea, increased work of breathing, and diffuse rhonchi. He continues to repeat the phrase "I don't know" and scratches the right side of his head repeatedly. The ED clinicians consult Psychiatry due to Mr. B's confusion and because his nurse reports that his presentation is similar to a previous psychiatric hospitalization 9 years earlier.

What do you consider in your differential diagnosis?

a) nonconvulsive status epilepticus
b) stroke
c) neuroleptic malignant syndrome
d) delirium
e) catatonia

EVALUATION Complex comorbidities

Mr. B has a lengthy history of schizophrenia, chronic right-sided heart failure secondary to pulmonary hypertension, moderate chronic obstructive pulmonary disease, hypertension, type 2 diabetes mellitus, and prostatic adenocarcinoma after external beam radiation therapy.

His symptoms of schizophrenia had been stable on his long-standing outpatient psychotropic regimen of haloperidol,

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5 mg nightly; mirtazapine, 15 mg nightly, for appetite stimulation and insomnia; and trazodone, 100 mg nightly for insomnia. Mr. B has been receiving assertive community treatment (ACT) psychiatric services for schizophrenia; a nurse refills his pill box with his medications weekly. He does not have a history of medication nonadherence, and his nurse did not think he had missed any doses before the weekend.

He has acute changes in depressed mood, perseveration, and a Mini-Mental State Examination (MMSE) score of 26 (missing points for delayed recall and inability to construct a sentence), which indicates a cognitive assessment score on the low end of the normal range for people with at least an eighth grade education.

At the hospital, the psychiatrist diagnoses hypoactive delirium due to Mr. B's fluctuating attention and disorientation. She also recommends that Mr. B continue his outpatient psychotropic regimen, and adds oral haloperidol, 5 mg, as needed for agitation (his QTc interval is 451 ms; reference range for men <430 ms, borderline prolonged 431 to 450 ms, prolonged >450 ms).

An initial laboratory workup and electrocardiogram reveal that Mr. B has an elevated troponin level (0.21 ng/mL; reference range <0.04; 0.04 to 0.39 ng/mL is elevated above the 99th percentile of a healthy population), non-ST-elevation myocardial infarction type II, Q waves in lead III, arteriovenous fistula with right axis deviation, acute on chronic kidney failure (creatinine level of 2.1 mg/dL, up from baseline of 1.4 mg/dL; reference range 0.84 to 1.21 mg/dL), elevated brain natriuretic peptide (111 pg/mL; reference range <125 pg/mL), and an elevated lactate level of 5.51 mmol/L (reference range 0.5 to 1 mmol/L). He also has a mixed respiratory alkalosis and metabolic acidosis with increased anion gap, transaminitis (aspartate aminotransferase 149 U/L; reference range 10 to 40 U/L), and elevated alkaline phosphatase (151 IU/L; reference range 44 to 147 IU/L). Urinalysis shows moderate ketones and is negative for nitrite or leukocyte esterase.

A brain CT rules out stroke. A chest X-ray shows subtle left basilar reticular opacity with a follow-up lateral view showing no consolidation and prominent pulmonary vasculature without overt edema.

In the ED, Mr. B is determined to have decision-making capacity and is able to authorize all treatment. Cardiology is also consulted, and Mr. B is admitted to the cardiac intensive care unit (CCU) for cardiogenic shock with close cardiac monitoring.

The Psychiatry and Cardiology teams discuss the risks and benefits of continuing antipsychotics. Due to the imminent risk of harm to Mr. B because of his significant agitation in the ED, which required treatment with one dose of IM haloperidol, 5 mg, and lorazepam, 2 mg, and close monitoring, the teams agree that the benefits of continuing haloperidol outweigh the risks.

On hospital Day 2, Mr. B's repetitive scratching resolves. He is moved from the CCU to a general medical unit, where he begins to have episodes of mutism and negativism. By hospital Day 6, catatonia is suspected due to a MMSE of 6/30 and a Bush-Francis Catatonia Rating Scale (BFCRS) score of 14 for predominant stereotypy, perseveration, and withdrawal (***Table 1***, ***page 44***). The teams determine that Mr. B lacks decision-making capacity due to his inability to rationally manipulate information. His brother is contacted and authorizes all treatment, deferring decision-making to the medical teams caring for Mr. B.

Mr. B undergoes an EEG, which rules out nonconvulsive status epilepticus and is consistent with encephalopathy/delirium. Neuroleptic malignant syndrome (NMS) is considered but is less likely because Mr. B had been receiving a stable dose of haloperidol for several years, is afebrile, has stable vital signs, has no muscle rigidity, and no evidence of leukocytosis, creatine kinase elevation, myoglobinuria, hyperkalemia, hyperphosphatemia, thrombocytosis, or hypocalcemia.

continued

Clinical Point

Due to the imminent risk of harm to Mr. B because of his significant agitation, the benefits of continuing haloperidol outweigh the risks

Clinical Point

Mr. B undergoes an EEG, which rules out nonconvulsive status epilepticus and is consistent with encephalopathy/delirium

Table 1

Mr. B's BFCRS scores before and after a lorazepam challenge (2 mg IV) on hospital Day 6

	Before lorazepam challenge	20 minutes after lorazepam challenge
Excitement	0/3	1/3
Immobility/stupor	0/3	0/3
Mutism	0/3	0/3
Staring	1/3	0/3
Posturing/catalepsy	0/3	0/3
Grimacing	0/3	0/3
Echopraxia/echolalia	1/3	1/3
Stereotypy	3/3 Would rhythmically kick the end of the bed with both feet when saying a word	0/3
Mannerisms	0/3	0/3
Verbigeration	3/3	0/3
Rigidity	0/3	0/3
Negativism	0/3	0/3
Waxy flexibility	0/3	0/3
Withdrawal	1/3 Decreased eye contact	0/3
Impulsivity	1/3 Threw blankets and sheets off bed	3/3 Tried to climb out of bed
Automatic obedience	0/3	0/3
Mitgehen	0/3	0/3
Gegenhalten	0/3	0/3
Ambitendency	0/3	0/3
Grasp reflex	0/3	0/3
Perseveration	3/3 "hamburger, actor, rat"	0/3
Combativeness	0/3	0/3
Autonomic abnormality	1/3	1/3
TOTAL	**14**	**6**

BFCRS: Bush-Francis Catatonia Rating Scale

Based on these clinical findings, Mr. B is diagnosed with catatonia and delirium.

The authors' observations

Delirium, characterized by inattention and changes in mental status, is a syndrome due to acute brain dysfunction. It can be subclassified as hyperactive or hypoactive based on the change of activity. Simple catatonia is characterized by changes in behavior, affect, and motor function (with hyper- or hypoactivity). It may arise from gamma-aminobutyric acid hypoactivity, dopamine (D2) hypoactivity, and possibly glutamate *N*-methyl-D-aspartate (NMDA) hyperactivity.[1] Malignant catatonia is simple catatonia combined with autonomic instability and

hyperthermia, which is a life-threatening condition. The BFCRS is commonly used to assess symptoms.[2]

Both catatonia and delirium result in significant morbidity and mortality. The 2 conditions share signs and symptoms yet rarely are diagnosed at the same time. DSM-IV, DSM-IV-TR, and DSM-5 state that a diagnosis of catatonia due to another medical condition cannot be made exclusively in the presence of delirium.[3,4] DSM-IV and DSM-IV-TR required at least 2 criteria from 5 areas, including motoric immobility, excessive motor activity, extreme negativism or mutism, peculiarities of voluntary movement, and echolalia or echopraxia. Instead of grouping symptoms into clusters, DSM-5 requires 3 criteria of 12 individual symptoms.[3,4] A co-occurrence with a medical illness precludes using the DSM-5 "catatonia associated with another mental disorder (catatonia specifier)" with the "unspecified catatonia" diagnosis category.[4]

However, a growing body of literature suggests that delirium and catatonia can co-occur.[5,6] In 2017, Wilson et al[6] found that of 136 critically ill patients in the ICU, 43% (58 patients) had only delirium, 3% (4 patients) had only catatonia, 31% (42 patients) had both, and 24% (32 patients) had neither. In patients with both catatonia and delirium, the most common signs of catatonia were autonomic abnormalities (96%), immobility/stupor (87%), staring (77%), mutism (60%), and posturing (60%).

The differential diagnosis of catatonia is extensive and varied.[3,4] The most common psychiatric causes are mood disorders (13% to 31%) and psychotic disorders (7% to 17%).[7] Neuromedical etiologies account for 4% to 46% of cases.[7] The most common medical and neurologic causes are seizure disorder, acute intermittent porphyria, systemic lupus erythematosus, and drug-related adverse effects (particularly due to clozapine withdrawal, risperidone, and phencyclidine).[7]

A workup that includes physical examination, laboratory testing, and neuroimaging can be helpful to identify delirium and catatonia, but there is limited literature to guide identifying coexisting delirium and catatonia other than a blend of physical exam findings of delirium and catatonia. Electroencephalogram may be normal in primary catatonia or may show nonspecific changes in secondary catatonia.[8] Additionally, discharges in the frontal lobes and anterior limbic systems with diffuse background slowing and dysrhythmic patterns may be seen.[7] Neuroimaging with MRI can help to evaluate catatonia.[9] Laboratory testing such as creatine phosphokinase levels can be high in simple catatonia and are often elevated in malignant catatonia.[7] Considering the possible co-occurrence of delirium and catatonia is critical to providing good patient care because the 2 conditions are treated differently.

How would you treat Mr. B?

a) switch to a different antipsychotic
b) discontinue haloperidol
c) initiate a lorazepam challenge
d) evaluate for electroconvulsive therapy (ECT)
e) B and C
f) other

TREATMENT A balancing act

Over the next month, Mr. B alternates between appearing catatonic or delirious. When he appears more catatonic, the dose of lorazepam is increased, which results in increased impulsivity and agitation and leads to multiple interventions from the behavioral emergency response team. At times, the team must use restraints and haloperidol because Mr. B pulls out IV lines and is considered at high risk for falls. When Mr. B appears more delirious and the dose of lorazepam is decreased, he becomes more catatonic.

continued

Clinical Point

Considering the possible co-occurrence of delirium and catatonia is critical because the 2 conditions are treated differently

Clinical Point

The first-line treatment for catatonia is benzodiazepines, with IV preferred over IM, sublingual, or oral formulations

Table 2

Mr. B's BFCRS scores on hospital Day 22

Excitement	0/3
Immobility/stupor	0/3
Mutism	0/3
Staring	0/3
Posturing/catalepsy	0/3
Grimacing	0/3
Echopraxia/echolalia	0/3
Stereotypy	1/3
Mannerisms	0/3
Verbigeration	0/3
Rigidity	0/3
Negativism	0/3
Waxy flexibility	0/3
Withdrawal	0/3
Impulsivity	0/3
Automatic obedience	0/3
Mitgehen	0/3
Gegenhalten	0/3
Ambitendency	0/3
Grasp reflex	0/3
Perseveration	0/3
Combativeness	0/3
Autonomic abnormality	0/3
TOTAL	**1**

BFCRS: Bush-Francis Catatonia Rating Scale

Following the diagnosis of catatonia on Day 6, oral haloperidol is discontinued to further mitigate Mr. B's risk of developing NMS. On hospital Day 6, Mr. B improves significantly after a 2-mg IV lorazepam challenge, with a BFCRS score of 6. At this point, he is started on lorazepam, 1 mg IV 3 times a day.

On Day 7, based on the complicated nature of Mr. B's medical and psychiatric comorbidities, the treatment team considers ECT to minimize medication adverse effects, but Mr. B's medical condition is too tenuous.

On Day 7, lorazepam is decreased to 0.5 mg/0.5 mg/1 mg IV. On Day 9, it is further decreased to 0.5 mg IV 3 times a day because Mr. B appears to be more delirious. On Day 10, lorazepam is increased to 1 mg IV 3 times a day, and oral haloperidol, 2 mg as needed for agitation, is restarted after multiple nights when Mr. B had behavioral emergencies and was treated with IM haloperidol and lorazepam. On Day 11, lorazepam is decreased and switched from IV formulation to oral, 0.5 mg 3 times a day. On Day 13, oral haloperidol is increased to 2 mg twice a day because of overnight behavioral emergencies requiring treatment with IV haloperidol, 4 mg. On Day 17, oral haloperidol is increased to 2 mg in the morning and 3 mg every night at bedtime because Mr. B has increased morning agitation. On Day 19, oral lorazepam is increased to 1 mg 3 times a day because Mr. B appears more catatonic. On Day 21, oral haloperidol is consolidated to 5 mg every night at bedtime. On Day 31, oral lorazepam is increased to 2 mg/1 mg/1 mg because he appears more catatonic with increased stuttering and mannerisms. On Day 33, oral haloperidol is increased to 6 mg every night at bedtime because Mr. B has morning agitation.

Multiple lorazepam and haloperidol dose adjustments are needed to balance the situation: combating catatonia, addressing delirium, managing schizophrenia symptoms, and improving Mr. B's cardiac status. Finally, Mr. B is stabilized on oral lorazepam, 2 mg every morning, 1 mg every day at noon, and 1 mg every day at bedtime, and oral haloperidol, 6 mg every day at bedtime. This regimen, Mr. B has a BFCRS score of 1 (***Table 2***) and returns to his baseline mental status.

The authors' observations

Delirium and catatonia typically have different treatments. Delirium is routinely treated by addressing the underlying medical and environmental factors, and managing comorbid symptoms such as agitation and disturbing hallucinations by prescribing antipsychotics, restoring the sleep-wake cycle with melatonin, initiating nonpharmacologic behavioral management, and avoiding deliriogenic medications such as benzodiazepines, opioids, and steroids.[10]

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Related Resources

- Wilson JE, Carlson R, Duggan MC, et al. Delirium and catatonia in critically ill patients: the delirium and catatonia prospective cohort investigation. Crit Care Med. 2017;45(11):1837-1844.
- Catatonia Information Center. Penn State University. http://catatonia.org/.

Drug Brand Names

Amantadine • Symmetrel
Aripiprazole • Abilify
Carbamazepine • Carbatrol, Tegretol
Clozapine • Clozaril
Haloperidol • Haldol
Lorazepam • Ativan
Memantine • Namenda
Metoclopramide • Reglan
Mirtazapine • Remeron
Risperidone • Risperdal
Topiramate • Topamax
Trazodone • Desyrel
Valproate • Depacon, Depakene, Depakote

Clinical Point

Memantine may be considered for patients with catatonic schizophrenia or comorbid catatonia and delirium

Catatonia is managed by prescribing benzodiazepines (with or without ECT) and by avoiding dopamine antagonists such as antipsychotics and metoclopramide (which may worsen catatonia or precipitate malignant catatonia).

The first-line treatment for catatonia is benzodiazepines, with IV preferred over IM, sublingual, or oral formulations. Electroconvulsive therapy is commonly used with benzodiazepines and is effective in 85% to 90% of patients. For ECT, bitemporal placement and daily treatment with brief pulses are frequently used. It is also effective in 60% of patients who fail to respond to benzodiazepines. Thus, ECT should be considered within the first 48 to 72 hours of benzodiazepine failure.[7]

Amantadine, a NMDA antagonist, may be a possible treatment for catatonia. A case report published in 1986 described a patient who developed catatonia after the abrupt withdrawal of amantadine during neuroleptic therapy.[11] Memantine also may serve as a treatment for catatonia through glutamate antagonism. A review identified 25 cases of patients with catatonia who were treated with amantadine or memantine.[12] Oral amantadine was administered at 100 to 400 mg/d in divided doses, with lower doses for patients with diminished renal function.[12] Memantine was administered at 5 to 20 mg/d.[12] All patients showed improvement after 1 to 7 days of treatment.[12] Thus, memantine may be considered for patients with catatonic schizophrenia or comorbid catatonia and delirium. Although memantine was not considered in Mr. B's case, he would have been a good candidate for treatment with this agent.

There are also case reports of aripiprazole being used for catatonia in the context of psychosis or delirium in both adults and adolescents.[13-15] Other medications used in case reports for treating catatonia include carbamazepine, valproate, and second-generation antipsychotics.[7]

Because most of the literature on pharmacotherapy for catatonia consists of case reports or small case series, further research on medication management of catatonia and delirium is needed to guide treatment.

OUTCOME Multiple rehospitalizations

On Day 57, Mr. B is discharged to a skilled nursing facility due to significant deconditioning.

Bottom Line

Delirium and catatonia share signs and symptoms, yet rarely are diagnosed at the same time. Both conditions result in significant morbidity and mortality. An emerging literature supports the concurrence of these 2 syndromes and aids in their diagnosis and treatment. Comorbidity with other medical conditions, common with both delirium and catatonia, substantially complicates treatment; thus, additional research into new treatment approaches is critical.

He is discharged with continued follow-up with his ACT psychiatrist and nurse. Mr. B's catatonia remains resolved; however, he is unable to be safely managed at the skilled nursing facility.

During the next 7 months, he is readmitted to the ICU for acute on chronic hypoxic respiratory failure 5 times; his rehospitalizations are complicated by delirium due to cardiogenic shock and urosepsis. Mild hyperactive delirium re-emerges after worsening respiratory failure and contributes to falls in the skilled nursing facility.

Six months later, Mr. B continues to receive the initial hospital discharge lorazepam regimen of 2 mg every morning, 1 mg every day at noon, and 1 mg every night at bedtime. The Psychiatry team slowly tapers this to 0.5 mg twice daily.

On Day 5 of Mr. B's fifth hospital readmission, based on his advance directive, Mr. B's family implements the do-not-resuscitate and do-not-intubate orders. He is transitioned to comfort measures, and dies on Day 6 with his brother and the hospital chaplain present.

References

1. Northoff G. What catatonia can tell us about "top-down modulation": a neuropsychiatric hypothesis. Behav Brain Sci. 2002;25(5):555-577; discussion 578-604.
2. Bush G, Fink M, Petrides G, et al. Catatonia. I. Rating scale and standardized examination. Acta Psychiatr Scand. 1996;93(2):129-136.
3. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.
4. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
5. Oldham MA, Lee HB. Catatonia vis-à-vis delirium: the significance of recognizing catatonia in altered mental status. Gen Hosp Psychiatry. 2015;37(6):554-559.
6. Wilson JE, Carlson R, Duggan MC. Delirium and catatonia in critically ill patients: the delirium and catatonia prospective cohort investigation. Crit Care Med. 2017;45(11):1837-1844.
7. Fricchione GL, Gross AF, Huffman JC, et al. Chapter 21: Catatonia, neuroleptic malignant syndrome, and serotonin syndrome. In: Stern TA, Fricchione GL, Cassem NH, et al. Massachusetts General Hospital Handbook of General Hospital Psychiatry, 6th Ed. Philadelphia, PA: Saunders Elsevier; 2010:273-288.
8. Van der Kooi AW, Zaal IJ, Klijn FA, et al. Delirium detection using EEG: what and how to measure. Chest. 2015;147(1):94-101.
9. Wilson JE, Niu K, Nicolson SE, et al. The diagnostic criteria and structure of catatonia. Schizophr Res. 2015;164 (1-3):256-262.
10. Maldonado JR. Acute brain failure: pathophysiology, diagnosis, management, and sequelae of delirium. Crit Care Clin. 2017;33(3):461-519.
11. Brown CS, Wittkowsky AK, Bryant SG. Neuroleptic-induced catatonia after abrupt withdrawal of amantadine during neuroleptic therapy. Pharmacotherapy. 1986;6(4): 193-195.
12. Carroll BT, Goforth HW, Thomas C, et al. Review of adjunctive glutamate antagonist therapy in the treatment of catatonic syndromes. J Neuropsychiatry Clin Neurosci. 2007;19(4):406-412.
13. Huffman JC, Fricchione GL. Catatonia and psychosis in a patient with AIDS: treatment with lorazepam and aripiprazole. J Clin Psychopharmacol. 2005;25(5): 508-510.
14. Roberto AJ, Pinnaka S, Mohan A, et al. Adolescent catatonia successfully treated with lorazepam and aripiprazole. Case Rep Psychiatry. 2014;2014:309517.
15. Voros V, Kovacs A, Herold R, et al. Effectiveness of intramuscular aripiprazole injection in patients with catatonia: report on three cases. Pharmacopsychiatry. 2009; 42(6):286-287.

Clinical Point

Further research on medication management of catatonia and delirium is needed to guide treatment