Visual hallucinations and severe anxiety in the ICU after surgery

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After major surgery, Mr. B, age 42, has visual hallucinations of someone placing a drug in his IV line, and develops severe anxiety. What could be causing these symptoms?

CASE Anxiety in the ICU

Mr. B, age 42, an African American man, is admitted to the inpatient medical unit for surgical treatment of peritoneal carcinomatosis with pelvic exenteration. He has a history of metastatic rectal cancer, chronic pain, and hypertension, but no psychiatric history. Mr. B's postsurgical hospital stay is complicated by treatment-resistant tachycardia and hypertension, and he requires a lengthy stay in the ICU. In the ICU, Mr. B reports having visual hallucinations where he sees an individual placing a drug in his IV line. Additionally, he reports severe anxiety related to this experience. His anxiety and visual hallucinations are treated with coadministration of IV lorazepam, diphenhydramine, and haloperidol. These medications resolve the hallucinations, but his anxiety worsens and he becomes restless. He receives additional doses of IV haloperidol administered in 5 mg increments and reaching a cumulative 12-hour dose of 50 mg. Mr. B continues to report anxiety, so the psychiatry consultation-liaison (C-L) service is called.

What should be part of the diagnostic consideration for Mr. B's anxiety?

a) delirium
b) generalized anxiety disorder
c) primary psychotic disorder
d) neuroleptic malignant syndrome (NMS)
e) akathisia
f) all of the above

The authors' observations

Determining the cause of Mr. B's anxiety is challenging because of his prolonged medical course, comorbidities, and exposure to multiple pharmacologic agents. The consulting psychiatric team should consider potential medical, psychiatric, and drug-related etiologies.

From a medical perspective, in a postsurgical patient treated in the ICU, the

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consulting practitioner must pay particular attention to delirium. ICU delirium is common—one report indicated that it occurs in 32.3% of ICU patients[1]—and frequently confused with psychiatric morbidity.[2] Identifying delirium as the cause of impairment is important because delirium has potentially modifiable underlying etiologies. Symptomatically, delirium presents as impairment and fluctuation in attention, awareness, and at least one other cognitive domain, with a clear indication that the impairment occurred over a short period of time and represents a departure from baseline.[3] In Mr. B's case, these symptoms have not been excluded and should be considered by the C-L psychiatrists.

In addition to delirium, the C-L team must consider psychiatric comorbidity. Mr. B has no psychiatric history and a sudden first occurrence of hallucinations; therefore, it is unlikely that he has developed a primary psychotic disorder. Because he reported his symptoms had been present only for several days, he would not meet criteria for schizophrenia, which according to DSM-5 criteria require at least 1 month of ≥2 symptoms (including delusions, hallucinations, disorganized speech, disorganized behavior, or negative symptoms) and 6 months of declining function.[3] However, although it is improbable, the C-L team must consider a primary psychotic illness, particularly given the potential devastating consequence of being misdiagnosed and mismanaged for an alternative illness. Unlike psychotic disorders, anxiety disorders are significantly more prevalent in the U.S. general population than primary psychotic disorders.[4] Furthermore, the prevalence of anxiety disorders increases in the ICU setting; one study found that up to 61% of ICU patients setting experience "anxiety features."[5] Therefore, anxiety disorders and stress disorders should be considered in ICU patients who exhibit psychiatric symptoms.

Clinicians also should consider medication-induced adverse effects. In the ICU, patients are frequently managed on multiple medications, which increase their risk of developing adverse effects and adverse reactions.[6] One potential consequence of polypharmacy is delirium, which remains a relevant potential diagnosis for Mr. B.[7] Alternative consequences vary by medication and their respective pharmacodynamics. We take into consideration Mr. B's exposure to high doses of the high-potency antipsychotic agent, haloperidol. Exposure to haloperidol can result in extrapyramidal symptoms, including akathisia,[8,9,10] and the rare, but potentially fatal, NMS.[11] These reactions can often be distinguished by taking a thorough history and a physical evaluation. In the case of akathisia, the clinician should look for medication exposure, titration, or taper. Most commonly, akathisia occurs secondary to antipsychotic exposure,[12] followed by the onset of a combination of subjective symptoms, such as restlessness, anxiety, and irritability, and an objective symptom of increased motor activity.[3] NMS, on the other hand, is distinguished by symptoms that include hyperthermia (>38°C), diaphoresis, severe rigidity, urinary incontinence, vital instability, alterations in mental health status, and elevations in creatine kinase greater than 4-fold the upper limit, usually in the setting of treatment with antipsychotics.[3] Nearly all cases of NMS occur within the first 30 days of antipsychotic exposure.[3] While, overtly, NMS may appear to be less subtle than akathisia, clinicians should still be weary to rule out this admittedly rare, though potentially lethal diagnosis, especially in an ICU patient, where the diagnosis can be muddied by medical comorbidities that may mask the syndrome.

Clinical Point

In the case of akathisia, the clinician should look for medication exposure, titration, or taper

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EVALUATION Focus on akathisia

On interview by the C-L team, Mr. B is visibly restless, moving all 4 extremities. He reports increased anxiety and irritability over the past 2 to 3 days. Mr. B states that he is aware

Table 1

Variations of akathisia and their characteristics

Entity	Description
Medication-induced acute akathisia	Presents as a combination of subjective anxiety/irritability and objective excessive movement (fidgeting, rocking, pacing) in the setting of the start, titration, or taper of medication (antipsychotic)[3,16,17]
Tardive akathisia	The late presentation of akathisia symptoms during the course of treatment, despite there being no change in the suspected medication (antipsychotic). These symptoms may not improve upon medication discontinuation[3,16,17]
Chronic akathisia	The chronic persistence of the symptoms of akathisia. Usually these symptoms tend to be objective, with subjective symptoms decreasing severity/remitting over time[16,17]
Withdrawal akathisia	The new development of akathisia in the setting of antipsychotic withdrawal[15]
Pseudoakathisia	The presence of objective akathisia symptoms, but not subjective symptoms, in the setting of treatment (most commonly antipsychotic). Usually these symptoms present late through the course of treatment. This diagnosis is controversial because some feel that it can represent a various diagnoses, including tardive dyskinesia, tardive akathisia, or chronic akathisia[14,16]

Source: References 3,14-17

of his increased motor movements and can briefly suppress them. However, after several seconds, he again begins spontaneously fidgeting, moving all 4 extremities and shifting from side to side in bed, saying, "I just feel anxious." He denies having visual hallucinations, and says that the previous hallucinations had spontaneously presented and remitted after surgery. He denies the use of psychotropics for mental illness, prior similar symptoms to this presentation, a family history of mental illness, recent illicit substance use, or excessive alcohol use prior to presentation. This history is corroborated by collateral information from his brother, who was present in the ICU. On physical examination, Mr. B is afebrile and his vital signs are within normal limits. He does not have muscular rigidity or neck dystonia. His laboratory values, including complete blood count, electrolytes, liver function tests, and creatine phosphokinase, are within normal limits.

His medication administration record includes 46 standing agents, 16 "as-needed" agents, and 8 infusions. Several of the standing agents had psychotropic properties; however, the most salient were several opioids, ketamine, midazolam, lorazepam, dexamethasone, haloperidol, and olanzapine.

What is the most likely diagnosis and cause of Mr. B's symptoms?

a) akathisia secondary to haloperidol
b) NMS secondary to haloperidol
c) akathisia secondary to midazolam
d) NMS secondary to midazolam

The authors' observations

We determined that the most likely diagnosis for Mr. B's symptoms was medication-induced akathisia secondary to haloperidol. Akathisia, coined by Haskovec in 1901,[12,13] is from Greek, meaning an "inability to sit."[12] DSM-5 describes 2 forms of akathisia: medication-induced acute akathisia, and tardive akathisia.[3] In the literature, others have described additional classifications, including chronic akathisia, withdrawal akathisia, and pseudoakathisia (***Table 1***[3,14-17]). In Mr. B's case, given his sudden development of symptoms and their direct chronologic relationship to antipsychotic treatment, and his combined subjective and objective symptoms, we believed that Mr. B's symptoms

Clinical Point

NMS may appear to be less subtle than akathisia and clinicians should still be weary to rule out this diagnosis, especially in an ICU patient

Clinical Point

High-potency antipsychotics are believed to remain the greatest risk factor for akathisia

were consistent with medication-induced acute akathisia (MIA). The identification and treatment of this clinical entity is important for several reasons, including reducing patient morbidity and maximizing patient comfort. Additionally, because akathisia has been associated with poor medication adherence, increased agitation/aggression, increased suicidality, and the eventual development of tardive dyskinesia,[18] it is a relevant prognostic consideration when deciding to treat a patient with antipsychotics.

Pathophysiologically, we have yet to fully shed light on the exact underpinnings of akathisia. Much of our present knowledge stems from patient response to pharmacologic agents. While dopamine blockade has been linked to akathisia, the exact mechanism is not completely understood. Previous theories linking nigrostriatal pathways have been expanded to include mesocortical and mesolimbic considerations.[12,17,18] Similarly surmised from medication effects, the transmitters *y*-aminobutyric acid, serotonin/5-hydroxytryptamine (5-HT), norepinephrine, and acetylcholine also have been linked to this syndrome, though as of yet, exact gross pathophysiologic mechanisms have not been fully elucidated.[12] More recently, Stahl and Loonen[19] described a novel mechanism by which they link the shell of the nucleus accumbens to akathisia. In their report, they indicate that the potential reduction in dopaminergic activity, secondary to antipsychotic administration, can result in compensatory noradrenergic activation of the locus coeruleus.[19] The increased noradrenergic activity results in the downstream activation of the shell of the nucleus accumbens.[19] The activation of the nucleus accumbens shell, which has been linked to unconditioned feeding and fear behavior, can then result in a cascade of effects that would phenotypically present as the syndrome we recognize to be akathisia.[19]

Numerous etiologies have been linked to MIA. Of these, high-potency antipsychotics are believed to remain the greatest risk factor for akathisia,[18] although atypical antipsychotics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, have been linked to the disorder.[18,19]

Regarding antipsychotics, risk factors for akathisia include drug potency, dose, and rapidity of titration.[20] All of these factors were relevant in our patient's case. Risk across antipsychotic classes is not well understood; few head-to-head studies have comparing antipsychotics. However, general estimates suggest a 15% to 40% prevalence in patients exposed to typical antipsychotics, as compared with 0% to 12% exposed to atypical antipsychotics.[8] The literature-reported difference in risk, as well as our patient's comparative difference in exposure to large doses of haloperidol (50 mg) as compared with 1 dose of olanzapine (5 mg), led us to believe his akathisia developed primarily due to his exposure to haloperidol. Conclusively linking his symptoms to haloperidol alone, however, is not possible, and we did consider that olanzapine may in fact have had some effect in worsening Mr. B's akathisia.

Which of the following is a treatment option for medication-induced akathisia?

a) propranolol
b) benztropine
c) mirtazapine
d) clonazepam
e) all of the above

The authors' observations

While there are reports on the efficacy of various agents in the treatment of akathisia, the most commonly evaluated agents are propranolol, anticholinergics, and benzodiazepines.[17,21]

Propranolol is a nonselective beta-adrenergic blocker with numerous indications.[17] Despite a 2004 Cochrane Review indicating that there is no evidence in support of central acting beta-blockers for treating

Table 2

Mr. B's Barnes Akathisia Scale score before and after treatment with IV diphenhydramine

Measure	Pre-intervention	2 hours after first intervention (50 mg)	4 hours after first intervention (50 mg) and 2 hours after second intervention (25 mg)	Day 2 of follow-up
Objective symptoms	3	0	0	0
Awareness of restlessness	2	1	0	0
Distress related to restlessness	3	1	0	0
Summed objective/ subjective symptoms	8 out of 9	2 out of 9	0 out of 9	0 out of 9
Global clinical assessment of akathisia	5	1	0	0

akathisia,[22] propranolol is not yet recognized as an appropriate treatment.[17] The reason for this discrepancy is likely due to the Cochrane Review's restrictive inclusion criteria, which prevented the analysis of much of the literature.[22] In fact, several reports cite evidence for the treatment efficacy of propranolol[17] and, to date, some reports continue to advocate for its use as a first-line agent in the treatment of akathisia. Admittedly, besides the Cochrane Review,[22] other reports have found propranolol to be ineffective for treating akathisia,[23] although these tend to be limited by their population size and generalizability.

As with propranolol, a 2006 Cochrane Review found "no reliable evidence to support or refute" using anticholinergic agents in the treatment of akathisia.[24] We suspect that the review's findings were likely secondary to its strict inclusion criteria.[24] In fact, several reports support using anticholinergic agents for treating akathisia.[25] Here we focus on benztropine and diphenhydramine.

Two reviews—Blaisdell[26] (1994) and Poyurovsky[27] (2010)—suggest modest benefits from benztropine, primarily in patients with comorbid Parkinson's disease. Despite these benefits, head-to-head trials seem to either point to the superiority of propranolol or to no difference between these agents for treating akathisia.[28,29] In a review, we only found 1 trial demonstrating benztropine's superiority over propranolol,[23] but this trial was constrained by its small population (6 patients). Therefore, the data suggest that, when indicated, clinicians should lean towards using propranolol for treating akathisia.

Diphenhydramine, a first-generation antihistamine with antimuscarinic properties, has been studied for its efficacy in treating metoclopramide-induced akathisia in the emergency setting.[30] There are several reports on the efficacy of this agent, including a large randomized study involving 281 patients that found it effective for preventing metoclopramide-induced akathisia.[30] Another head-to-head trial reported the benefit of the diphenhydramine vs midazolam.[31] Both agents were efficacious for treating akathisia; however, midazolam had a more rapid onset. Despite these positive reports, double-blind trials have found diphenhydramine to be

Clinical Point

When indicated, clinicians should lean toward using propranolol for treating akathisia

Related Resources

- Factor SA, Leffler JB, Murray CF. Drug-induced movement disorders: a clinical review. Medscape. http://www.medscape.org/viewarticle/586881.
- Marder S, Stroup TS. Pharmacotherapy for schizophrenia: side effect management. UpToDate. https://www.uptodate.com/contents/pharmacotherapy-for-schizophrenia-side-effect-management.

Drug Brand Names

Amantadine • Symmetrel
Benztropine • Cogentin
Clonazepam • Klonopin
Clonidine • Catapres
Dexamethasone • Decadron
Diazepam • Valium
Diphenhydramine • Benadryl
Gabapentin • Neurontin
Haloperidol • Haldol
Ketamine • Ketalar
Lorazepam • Ativan
Metoclopramide • Reglan
Mianserin • Tolvon
Midazolam • Versed
Mirtazapine • Remeron
Olanzapine • Zyprexa
Propranolol • Inderal
Rivastigmine • Exelon
Trazodone • Oleptro

Clinical Point

Benzodiazepines have also been found to be efficacious for treating akathisia

ineffective,[17] which suggests propranolol should be the first-line agent, assuming it is not contraindicated.

Benzodiazepines have also been found to be efficacious for treating akathisia. A 1999 Cochrane Review included 2 randomized controlled trials that assessed the efficacy of clonazepam vs placebo for treating akathisia.[32] It found evidence of benefit for clonazepam, but questioned the generalizability of these studies.[32] This review did not include several other reports that suggest benefits of other benzodiazepines for treating akathisia. Other than clonazepam, reports suggest benefit for diazepam, lorazepam, and midazolam for treating akathisia.[17] Despite this evidence and the findings from this Cochrane Review, the literature does not appear to point to clear dominance of these agents over propranolol. Given the safety concerns when prescribing benzodiazepines, it would be prudent to utilize propranolol as a first-line agent for treating akathisia.

Finally, other reports have cited treatment efficacy linked to serotonin 2A receptor (5-HT2A) antagonists (mianserin, mirtazapine, and trazodone), clonidine, gabapentin, amantadine, and other agents.[17] If treatment with propranolol is ineffective or contraindicated, clinicians should utilize their clinical judgement in deciding on the use of one agent over another.

OUTCOME Complete resolution

Haloperidol is discontinued and diphenhydramine, 50 mg IV, is administered. (Diphenhydramine was used instead of propranolol due to immediacy of availability.) Most of Mr. B's signs and symptoms resolve on a repeat interview 3 hours later. He receives another dose of diphenhydramine, 25 mg IV, for persistent mild irritability. By Day 2 of follow-up, his symptoms completely resolve as measured on the Barnes Akathisia Scale[33] (***Table 2, page e5***).

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continued

Bottom Line

Akathisia is an elusive adverse effect of antipsychotics and can be misdiagnosed as anxiety. Close consideration should be given to potential medical, psychiatric, and drug-related etiologies in patients who have a prolonged medical course, comorbidities, and exposure to multiple pharmacologic agents.

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Clinical Point

Given the safety concerns with benzodiazepines, it would be prudent to use propranolol as a first-line agent for treating akathisia