Treatment of Acute Agitation Associated With Excited Catatonia Using Dexmedetomidine:

Case Series and Literature Review

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Psychomotor agitation is a common presentation in psychiatric and medical settings. It presents with symptoms of restlessness, irritability, anxiety, and increased or excessive movement that can culminate with aggressive or violent behaviors. It can be a manifestation of decompensated thought disorders, mood disorders, substance use, and medical or neurologic illnesses.

Antipsychotics, frequently used to control psychomotor agitation, are relatively contraindicated in catatonia, a neuropsychiatric syndrome that comprises motor and behavioral signs and symptoms. Despite the fact that catatonia was first described in the late 1800s, it remains vastly underrecognized in both general and psychiatric settings,[1] even by seasoned psychiatrists. As a consequence, many patients end up receiving suboptimal and potentially harmful treatment.

More than half of catatonic patients may go undiagnosed on admission, and one-third of them remain undiagnosed after receiving a psychiatric consultation. Clinicians must have a high index of suspicion and familiarity with the syndrome, as many of its features (eg, agitation, grimacing, echolalia, perseveration) are also commonly seen in other psychiatric conditions that are typically treated with antipsychotic medications (eg, psychosis, mania, agitation secondary to substance use or medical conditions). Excited catatonia, a subtype of catatonia also known as delirious mania, is a neuropsychiatric syndrome characterized by rapid onset of delirium (altered sensorium, attention deficits, and confusion), mania (grandiosity, emotional lability, decreased sleep, psychomotor agitation), and psychosis. It remains significantly unrecognized two centuries after it was first described.[2] The Bush-Francis Catatonia Rating Scale (BFCRS)[3] is a standardized assessment designed to screen and diagnose catatonia. Consisting of 23 items, it is a reliable and validated tool that takes approximately 5 minutes to administer and is currently the preferred rating scale for the detection of catatonia.[4]

Dexmedetomidine is a promising option to treat agitation in catatonia.[5] It is a highly selective α_2-receptor agonist that has similar affinity at each of the 3 receptor subtypes (Table 1). Approved by the US Food and Drug Administration in 1999 for short-term (< 24 hours) analgesia and sedation in the intensive care unit (ICU), dexmedetomidine's current indications include sedation of intubated and mechanically ventilated patients during treatment in an intensive care setting and nonintubated patients prior to and/or during surgical and other procedures. It is administered as a loading dose of 1 μg/kg over 10 to 20 minutes followed by a continuous infusion of 0.2–0.7 μg/kg/h. The most frequently observed adverse effects are hypotension, respiratory depression, bradycardia, dry mouth, and nausea. Relative contraindications to the use of dexmedetomidine include a known sinus node or atrioventricular node dysfunction, patients who cannot mount a stress-induced stimulation of the sympathetic nervous system, and those with limited sympathetic reserve.[6] For that reason, it should be used with caution in patients with comorbid heart disease or when given with other medications that possess negative chronotropic effects. It is considered safer than other benzodiazepines due to its limited potential for causing apnea or respiratory depression and in light of its ideal characteristics including rapid onset, minimal side effects, and noninvasive administration technique.

Case 1

A 30-year-old woman with no prior medical or psychiatric history was brought to the emergency department (ED) for an abrupt onset of confusion and disorientation. In the ED, she exhibited marked anxiety and paranoia and reported auditory and visual hallucinations. Severe psychomotor agitation led to physical aggression toward ED staff, and she required medication restraints with haloperidol and lorazepam. She was admitted to the inpatient psychiatric unit, where she also displayed manic symptoms of

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Table 1. Characteristics of Dexmedetomidine

Short duration of action (minutes) and a rapid distribution phase with a distribution half-life ($t_{1/2}$) of approximately 6 minutes, a terminal elimination half-life ($t_{1/2}$) of approximately 2 hours, and steady-state volume of distribution of approximately 118 L.
Clearance estimated to be approximately 39 L/h (the mean body weight associated with this clearance estimate was 72 kg).
The average protein binding was 94% and was constant across the different plasma concentrations tested.
Metabolism: almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces.
Dosage modifications: geriatric patients (recommended intravenous loading infusion dosage of dexmedetomidine for initiation of procedural sedation is 0.5 µg/kg infused over 10 minutes); patients with hepatic impairment (consider dosage reduction of dexmedetomidine for initiation of procedural sedation and maintenance of procedural sedation); and due to drug interactions (when coadministered with anesthetics, sedatives/hypnotics, or opioids, consider dosage reduction).

hypersexuality, hyperreligiosity, impulsivity, and insomnia. The initial laboratory workup including a urine toxicology and blood alcohol level, complete blood count, basic metabolic panel, liver function tests, HIV assay, urine human chorionic gonadotropin, and thyroid studies was unremarkable. She was started on risperidone 0.5 mg twice daily, gradually increased to 2 mg twice daily, after which her condition quickly deteriorated. Over the next 3 days, her symptoms of psychomotor agitation, impulsivity, auditory and visual hallucinations, and intense mood dysregulation increasingly worsened. She became loud and combative, started to exhibit purposeless movements, and tried to elope on multiple occasions. A diagnosis of excited catatonia was made, corroborated by an elevated score of 30 on the BFCRS that decreased to 3 after she received 2 mg of intramuscular (IM) lorazepam.

She was started on valproic acid and high doses of lorazepam (up to 12 mg/d), and a recommendation was made to avoid antipsychotics, but, because she remained severely disruptive and was putting other patients and staff at risk, she required a few doses of as-needed olanzapine and chlorpromazine. After each dose of the antipsychotics, however, she became more agitated, violent, loud, and hypersexual, at times requiring physical restraints. She showed mental status fluctuations and autonomic dysregulation, accompanied by creatine kinase and transaminase elevation. Due to the profound level of behavioral dysregulation and persistent patent suffering that was refractory to the available psychopharmacologic treatment options, she was transferred to the intensive care unit (ICU) for treatment with intravenous (IV) sedation with dexmedetomidine. Dexmedetomidine was administered at a loading dose of 1 µg/kg over 10 minutes followed by a maintenance infusion of 0.5 µg/kg/h. The patient immediately calmed down and had no further episodes of agitation that required physical or chemical restraints or spot doses of antipsychotics. Repeat vital signs obtained 15 minutes after the dexmedetomidine loading dose were within normal limits. This intervention allowed all antipsychotic medications to be discontinued, leading to rapid improvement of all clinical and laboratory parameters, including a significant drop in creatine kinase (CK) level and normalization of vital signs.

While the patient was comfortably sedated, a comprehensive medical workup, not feasible previously due to intense agitation, was performed (which was unremarkable) and an emergency order for electroconvulsive therapy (ECT) was obtained. She returned to her baseline condition after 3 ECT treatments and was discharged home.

Case 2

A 45-year-old woman with a history of bipolar disorder was brought to the ED by paramedics for erratic behavior and psychomotor agitation. On arrival in the ED, she displayed violent behaviors, yelling, cursing, and swinging a closed fist at health care providers, and had to be chemically restrained with IM haloperidol and lorazepam.

The initial laboratory evaluation was unremarkable. The patient was admitted to the inpatient ward for management of acute mania. After receiving treatment with quetiapine (0.5 mg twice daily, gradually increased to 2 mg twice daily) for 4 days, she became increasingly agitated, restless, disoriented, aggressive, and impulsive, at one point jumping off her bed and striking her head.

A diagnosis of excited catatonia was made, as she displayed perseverative speech, purposeless repetitive movements, odd posture, gegenhalten, and combativeness. Due to the patient's agitation, she required physical restraints and received IM lorazepam 2 mg every 6 hours and oral zolpidem, with no discernible effect. Given persistent symptoms, the staff expressed safety concerns and requested a dose of an antipsychotic. Chlorpromazine 50 mg IM was administered, leading to a 3-hour period of calmness that allowed for the removal of restraints and the obtainment of a head computed tomography (CT) scan (which showed no acute findings), but she then again became severely agitated, with persistent tachycardia (100–120 bpm), low-grade fever (99.9°F [axillary]), intense diaphoresis, and muscle rigidity. An unproductive attempt was made overnight to transfer the patient to the ICU for active cooling and IV sedation with appropriate monitoring. In the morning, when the patient was assessed by her regular team and an internal medicine consultant, she was successfully transferred to the ICU for treatment of possible malignant catatonia/neuroleptic malignant syndrome. On day 1 of her ICU admission, she was started on IV lorazepam 2 mg every 4 hours and IV dexmedetomidine 0.4 µg/kg/h. Due to breakthrough agitation, aggression, and impulsivity, this dosage was gradually increased by day 2 of ICU admission to IV lorazepam 2 mg every 2 hours and dexmedetomidine 1.2 µg/kg/h. IV phenobarbital and valproic acid were added in an attempt to treat her underlying bipolar disorder and breakthrough agitation while avoiding antipsychotics. While in the ICU, she continued to have low-grade fever (up to 100°F) and displayed intermittent rigidity on examination. BFCRS scores ranged from 20 to 25.

After extensive discussion with the family, there was eventual agreement from the patient's health care proxy for

ECT treatment. Bilateral ECT was performed on day 4 of ICU admission, and she was transferred to the medicine service the following day, when she showed dramatic improvement of her symptoms and had a score of zero on the BFCRS.

After the fourth ECT treatment, the patient appeared euthymic and back to her baseline condition. She received a total of 6 ECT treatments over the span of 11 days, which she tolerated well.

Case 3

An 18-year-old man was brought to the emergency department by the police after 2 weeks of aggression toward family members and inability to care for himself. His only psychiatric history was a recent psychiatric hospitalization for bizarre behavior following reported marijuana ingestion. He was diagnosed with psychosis and prescribed haloperidol 5 mg twice daily, which he self-discontinued after discharge. In the ED, the patient endorsed auditory hallucinations, spoke nonsensically, and consistently attempted to get out of bed. He tried to elope and assault staff multiple times, requiring physical restraints for extended periods. During a prolonged ED stay while waiting for a psychiatric hospital bed, he received multiple chemical restraints. Laboratory tests were significant only for a serum creatinine kinase level of 6,500 IU/L and a urine drug screen positive for cannabinoids. The patient developed coffee-ground emesis after ingesting a metal screw while in the ED, requiring a medical admission. During this admission, the patient was started on olanzapine 20 mg nightly with concern for psychosis. He required multiple medication restraints and 2:1 observation. Initial concerns for excited catatonia were raised after echopraxia was documented by a psychiatry consultant.

After medical clearance, the patient was transferred to an inpatient psychiatric unit. There, he was continuously pacing, intermittently aggressive with staff, and speaking nonsensically. He was started on valproic acid 20 mg/kg/d, olanzapine 15 mg twice a day, and lorazepam 2 mg 4 times a day, with quetiapine and lorazepam as needed for agitation. He often attempted to enter other patients' rooms and touch staff despite redirection. He continued to require multiple medication restraints for threatening behaviors and posturing at staff. During one post-medication restraint examination, echolalia was observed. Vital signs were remarkable for a blood pressure of 160/94 mm Hg with heart rate of 115 bpm, signaling autonomic instability.

He required 4 separate restraints for aggression toward staff that day, including two with antipsychotics (ziprasidone 20 mg and chlorpromazine 50 mg), both in addition to lorazepam. Even though the patient appeared sedated, slurring words with eyes intermittently closing, he continued to swing his arms aggressively at staff. His BFCRS score was 12, and he scored points for mutism (1), echolalia (1), excitement (2), impulsivity (3), combativeness (3), and autonomic instability (2). The ICU was consulted given intractable agitation, inability to closely monitor vital signs, and high concern for excited catatonia.

In the ICU, the patient was placed on lorazepam 1 mg IV every 2 hours and an IV dexmedetomidine drip. The dose of dexmedetomidine varied between 0.4 and 1.8 μg/kg/min, as the patient intermittently started pulling at lines. The dose was titrated to the patient's being calm but awake. The patient was kept in the ICU on dexmedetomidine for 5 days until transport to an external facility for ECT was arranged. The patient was able to be weaned from dexmedetomidine after 2 ECT sessions and discharged home after 6 ECT sessions while at baseline condition.

Case 4

A 23-year-old man with a prior psychiatric history significant only for cannabis and stimulant use disorder was brought to the ED by paramedics for acute mental status changes including aggression and confusion. There, he was severely agitated and actively hallucinating and required physical and medication restraints with IM haloperidol 5 mg and lorazepam 2 mg, with good but transient results. His initial evaluation was significant for a toxicology screening positive only for cannabinoids. All other laboratory values were unremarkable. He did not cooperate with an electrocardiogram (ECG) or neuroimaging tests. Vital signs showed heart rate of 120–140 mm Hg, blood pressure of 130/85 bpm, and respiratory rate of 18 breaths per minute. Physical examination was relevant for dilated and minimally reactive pupils.

He was admitted to the inpatient psychiatric unit with a presumptive diagnosis of substance-induced psychosis versus anticholinergic delirium, and he was started on risperidone 0.5 mg twice daily and then increased to 2 mg twice daily, but was mostly noncompliant. He remained combative, uncooperative, and difficult to redirect. His behaviors escalated and started to comprise physical assaults to the nursing staff, and the patient ended up receiving a few as-needed doses of IM haloperidol 5 mg and lorazepam 2 mg, with very short-term benefit. He became increasingly restless and hyperactive and diaphoretic, displaying purposeless movements, echopraxia, stereotypies and mannerisms, and verbigeration. He also showed autonomic instability, with a blood pressure of 150/85 mm Hg and a pulse of 140 bpm. His BFCRS score was 25. All antipsychotics were immediately discontinued, and the patient was subsequently transferred to the ICU for treatment with IV dexmedetomidine, started at a loading dose of 1 μg/kg over 10 minutes followed by an infusion of 1 μg/kg/h. The patient quickly calmed down and allowed for further medical investigation including a head CT scan (unremarkable) and an ECG, which showed a prolonged corrected QT interval (QTc) of 478 ms (reference range, < 450 ms), possibly from exposure to QTc-prolonging agents that were used as an attempt to control his agitation. By the second day in the ICU, his behavior was well-controlled and physical or medication restraints were not required. Vital signs quickly normalized after discontinuation of the offending agents. The patient was started on lorazepam 2 mg 6 times a day, a dose that was gradually tapered down after day 3. He was discharged home on day 5 at his baseline

condition. The patient eventually admitted to using an over-the-counter cold medication containing dextromethorphan as well as smoking synthetic marijuana that was likely mixed with other unknown substances at a recreational event 1 day prior to presentation.

Discussion

Numerous acute psychiatric presentations, either from underlying primary mental illness or secondary to medical conditions or substance use, include severe psychomotor agitation that is frequently difficult to contain. Diagnostic clarity in those cases is essential, as treatment options may substantially differ. Among the many possible etiologies, catatonia is an entity that historically has been underrecognized.

Catatonia is highly prevalent in general and psychiatric hospitals, with a prevalence that can reach 17%,[7] but remains underdiagnosed 2 centuries after it was first described,[8] even in psychiatric settings and even when a psychiatric consultation has been obtained.[9] More than half of catatonic patients may go undiagnosed on admission, and one-third of them remain undiagnosed after receiving a psychiatric consultation. Clinicians must have a high index of suspicion and familiarity with the syndrome, as many of its features (eg, agitation, grimacing, echolalia, perseveration, combativeness) are also commonly seen in other psychiatric conditions that are typically treated with antipsychotic medications (eg, psychosis, mania, agitation secondary to substance use or medical conditions, organic delirium). Excited catatonia, a subtype of catatonia also known as delirious mania, is a neuropsychiatric syndrome characterized by rapid onset of delirium (altered sensorium, attention deficits, mental status fluctuations, and confusion), mania (grandiosity, emotional lability, decreased sleep, and psychomotor agitation), and psychosis. It has been reported that approximately 20% of patients with acute mania show signs of delirium and meet criteria for catatonia,[10] but a significant percentage of these cases end up being misdiagnosed as acute episodes of organic delirium.[11]

In our clinical practice, and in communication with colleagues from various parts of the world, we have noticed an increase in presentations similar to the ones we described. We suspect the cause for this increase to be multifactorial:

- Anticholinergic toxindromes have become very prevalent, with approximately 90,000 calls made to poison control centers for antihistamine and related anticholinergic exposures each year in the United States.[5] These include the increasing use of over-the-counter cold medications containing dextromethorphan.[12]
- New and synthetic psychoactive drugs, many of which are not routinely tested by usual toxicology screening, are being used and are often implicated in similar scenarios.
- Neuropsychiatric presentations of COVID-19 have been increasingly described in the literature, affecting a quarter of infected individuals and almost half of those severely ill with COVID-19, who show a high incidence of delirium.[13] A study of hyperactive delirium in people with COVID-19 including 10 systematic reviews noted that only quetiapine and dexmedetomidine showed significant benefits in that setting.[14]
- Familiarity with the various subtypes of catatonia is slowly expanding, thanks to changes in psychiatric training and the increasing tendency to value the neurobiological aspects of psychiatry.

Failure to correctly identify excited catatonia/delirious mania has important and potentially harmful repercussions. Moreover, the lack of an accurate diagnosis may incur use of much lower doses of benzodiazepines than what is usually required to treat catatonia, as well as delays in administering ECT. The use of antipsychotics in catatonia is controversial. Many consider them contraindicated due to the very elevated risk of leading to the progression of malignant catatonia or neuroleptic malignant syndrome, which carry a high rate of mortality and morbidity.[15,16] Benzodiazepines, even at high doses, are frequently ineffective in the management of acute psychomotor agitation or contribute to worsening delirium and/or disinhibition. Electroconvulsive therapy, the gold-standard treatment for catatonia, is not always available or feasible.

Dexmedetomidine, a drug first approved for use in adults in 1999 for sedation and agitation control of intubated and mechanically ventilated patients during treatment in an intensive care setting and nonintubated patients prior to and/or during surgical and other procedures, is a promising option to treat agitation in those psychiatric situations.[5] For a long time, its application in psychiatry was confined to the management of post-ECT agitation or delirium, a common occurrence affecting up to 12% of treatments.[17,18] Although post-ictal delirium often responds to benzodiazepines and/or propofol, dexmedetomidine has been used with increasing regularity for this indication due to its "delirium-sparing" properties.[18,19] In a study with post-cardiac surgery patients,[20] the incidence of delirium was 3% for patients receiving dexmedetomidine compared to 50% for those receiving propofol and 50% for patients receiving midazolam. When dexmedetomidine was used prophylactically before ECT, patients receiving it had significantly lower incidence of developing post-ictal delirium compared to those receiving placebo ($P < .001$).[21]

Causing minimal effect on respiratory function and cardiac rhythm, dexmedetomidine is becoming more widely used as a sedative agent in cases of psychomotor agitation related to anticholinergic overdoses, as it provides sedation, anxiolysis, and modest analgesia with minimal respiratory depression. It is shown to have antidelirium effects and promotes a natural sleep pattern while offering no anticholinergic activity,[13,22] and it has been increasingly used in the treatment of delirium in ICU or post-surgical settings. It has also been proposed

that dexmedetomidine could be a valuable addition in the treatment of complicated alcohol withdrawal delirium, a possibly fatal condition, decreasing the need for physical or medical restraints.[23] These positive experiences led to the addition of dexmedetomidine to the novel formulations for the management of acute agitation in patients with schizophrenia and bipolar disorder, an important development as it offers rapid and efficacious results and relatively few adverse effects.[24]

This case series and review alert to the importance of an early and accurate diagnosis of excited catatonia/delirious mania, as misdiagnosis can lead to substantial differences in management and consequently outcomes. The current work also supports the inclusion of dexmedetomidine in the arsenal of pharmacologic options to treat acute and severe psychomotor agitation in psychiatric settings, as it provides effective and fast sedation that allows for medical and psychiatric stabilization, clinical investigation that would not be possible otherwise, and optimal behavioral control while more definitive treatment is pursued.

Conclusions

With a benign hemodynamic profile and minimal effect on respiratory function or QT prolongation,[25] dexmedetomidine presents as a promising and efficacious option to treat psychomotor agitation in psychiatric settings, including excited catatonia (delirious mania), in which treatment with antipsychotics should typically be avoided and benzodiazepines may worsen delirium or contribute to respiratory depression.

We expect to see an increase in the number of cases of excited catatonia (delirious mania) in the context of the COVID-19 pandemic as well as secondary to increasing use of synthetic drugs that often go untested on routine toxicology screenings.[26] Many times, the patients are not even aware of the substances they are ingesting and thus are unable to disclose these ingestions to providers. These scenarios often pose ethical and clinical dilemmas, challenges, and obstacles that highlight the importance of developing a broad differential diagnosis when approaching an agitated, manic, psychotic, delirious, or restless patient.

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