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Catatonia and Schizophrenia in a Young Man with Autism Spectrum Disorder and Clozapine-Induced Myocarditis

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CASE HISTORY

PK was diagnosed with autism spectrum disorder (ASD) at age 4 with the Autism Diagnostic Observation Schedule. The diagnosis was made by an interdisciplinary team consisting of a child psychiatrist, neuropsychologist, pediatrician, and speech/language pathologist. PK was born full term with no complications. He demonstrated no delays in motor or language development. After the ASD diagnosis, he qualified for no services in school except help with socialization; he mainly had one or two friends during primary and secondary education. Growing up, PK was articulate and performed well in school, and he took special interest in computers. By the onset of symptoms described below, he was 20 years old, living at home with his mother and father, and attaining straight As in his college computer science classes. His only psychiatric diagnosis was ASD. There is no known family psychiatric history. He had no prior hospitalizations and no history of suicide attempts or self-injury. He was on no psychiatric medications. His only identified medical condition was hypothyroidism, for which he was taking levothyroxine.

PK's presentation began in October of 2018. His computer science professor, who was a family friend, noticed PK's increasing absences in the small class. When PK did come to class, he barely spoke, and he could no longer complete his classwork or his homework. Out of concern his professor reached out to PK's family.

PK then revealed to his mother that sometimes he drove to school and simply sat in his car for eight hours before returning home. His mother, who is a physician, also noticed other uncharacteristic behaviors. He began to eat less; initially, he skipped perhaps one meal each day, but between October 2018 and January 2019, this developed into a constant refusal to eat. During this time, PK made references that he could "see" nanotechnology; for example, although a toaster toasts bread, he could visualize the underlying mechanics. He also began to move less, and when he did move, his movements became less fluid and appeared mechanical.

In January of 2019, campus police found PK sitting alone in his car. He had vomited and urinated on himself. He could not tell them any identifying information, date, or time; emergency medical services subsequently admitted him to a local hospital. At that hospital catatonia syndrome was identified, but the team was unable initially to determine the etiology. At presentation, his Bush-Francis Catatonia Rating Scale (BFCRS) was 18; further detailed records are unavailable. He was initiated on lorazepam titrated to 1 mg three times daily (TID) while the local hospital conducted workup for inflammatory, infectious, neoplastic, or psychiatric causes of catatonia. Magnetic resonance imaging of the brain was negative, as was computerized tomography of the chest/abdomen/pelvis, and scrotal ultrasound. Electroencephalogram did not detect epileptiform activity, and lumbar puncture with cerebrospinal fluid analysis was unremarkable, including a negative autoimmune/paraneoplastic panel. The following antibodies were not detected: anti-thyroglobulin, antinuclear, human immunodeficiency virus, rheumatoid factor, rapid plasma reagin, and anti-neutrophil cytoplasm. Extractable nuclear antigen (ENA10) was also negative. Complete blood count, complete metabolic panel, liver function tests, lipid profile, and hemoglobin A1c were within normal limits. Thyroid-stimulating hormone was slightly elevated, but reflex-free T4 was within normal limits. Based on these results, the team was unable to identify a cause for PK's catatonia. After 12 days, the team felt catatonia had responded adequately to lorazepam 1 mg TID and that PK was stable enough to warrant discharge to our outpatient clinic.

PK's parents picked him up from the local hospital. But within 30 minutes of the car ride, it was clear that PK was not well. He suddenly began to pull his mother's hair, and his father was unable to intervene. This development was even more alarming as PK had never been aggressive before.

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PK's mother contacted us at this time, and we made immediate arrangements to transfer PK to another facility, which offered the use of their electroconvulsive therapy (ECT) capability, as we suspected it may be needed.

At this second facility, the team felt that his symptoms were better explained by major depressive disorder and aggression due to ASD. PK's lorazepam was increased from 1 mg TID to 2 mg TID for aggression, and risperidone 0.5 mg twice daily was added. He was initiated on escitalopram 10 mg for depression and discharged ten days after presentation.

We first encountered PK at our outpatient clinic in February 2019. His BFCRS was 22 on lorazepam 2 mg TID, which we noted was an increase compared to the previously documented score of 18. The most prominent symptoms we observed were displays of automatic obedience, waxy flexibility, and negativism. To target worsening catatonia, we increased lorazepam to 3 mg TID. We also took note of his psychotic symptoms and diagnosed schizophreniform disorder. As the catatonia symptoms were markedly severe compared to the psychotic symptoms, we targeted our initial treatment to improve catatonia. As risperidone may have exacerbated catatonia, we discontinued it. We also tried to arrange outpatient ECT, but he was declined by the performing physician because of the potential risks.

Finally, as we were unable to corroborate the diagnosis of major depressive disorder, we also discontinued escitalopram.

PK's catatonia syndrome responded to slow titration of lorazepam. By the time he was taking 5 mg lorazepam TID, his BFCRS was 8; most prominent was waxy flexibility. With lorazepam 6 mg TID, BFCRS was further reduced to 6, and waxy flexibility had not yet improved. Throughout February of 2019, as catatonia improved, his psychotic symptoms became increasingly apparent. He spoke more about nanotechnology but frequently bounced between topics, unable to describe his thoughts linearly—which was extremely incongruous with his previously articulate speech. He was observed many times sitting alone in his room, having an extensive discussion with "Lucy." Eventually, he threw a toaster at his father because his internal discussant commanded him to do so.

In response to these developments, we advised his mother to utilize olanzapine 2.5 mg orally disintegrating tablets as needed for aggressive behaviors having the potential to harm self or others. The olanzapine was slowly titrated to 5 mg nightly for psychotic symptoms.

We selected olanzapine rather than a different antipsychotic for several reasons. Risperidone appeared to have exacerbated catatonia, which would also be a concern with other potent D2 antagonists. Even a less potent D2 antagonist such as aripiprazole posed a risk of exacerbating excitatory catatonia features through akathisia. We also did not favor quetiapine, as its antipsychotic properties typically require high doses and prolonged titration.

As catatonia failed to lyse with lower doses of lorazepam, we increased it to 7 mg TID. This dose of lorazepam is quite high for the outpatient setting; however, as his mother is a physician, she regularly monitored his blood pressure and also monitored for adverse events.

Olanzapine did not appear to exacerbate catatonia, but he did refuse some doses of lorazepam. His mother did not notice any symptoms of benzodiazepine withdrawal, but in March 2019, the BFCRS increased to 10 (emergence of mitgehen-3). Thus, lorazepam was increased to 8 mg TID, and olanzapine to 7.5 mg nightly.

In late March 2019, the catatonia symptoms fully resolved (BFCRS 0), but he continued to demonstrate psychotic symptoms. Olanzapine was increased to 10 mg nightly, and lorazepam was continued at 6 mg TID. He tolerated olanzapine at this dose and continued to display resolution of catatonia. Olanzapine was then increased to 15 mg nightly for two weeks and then to 20 mg to target psychotic symptoms. However, he continued to report the voice of "Lucy" and seeing nanotechnology. His speech continued to lack its previously articulate composition; instead, it was more reflective of frankly disorganized thoughts.

After six weeks of olanzapine pharmacotherapy, the last of which was at 20 mg, PK's psychotic symptoms still did not respond. We needed to utilize an alternative agent. Now that catatonia symptoms were better controlled, we cross-titrated to a more potent D2 antagonist by re-selecting risperidone.

As of June 2019, the psychotic symptoms had lasted for longer than six months, and his diagnosis was updated to schizophrenia. By this point, three months of risperidone pharmacotherapy at 4 mg resulted in minimal, if any, improvements in psychotic symptoms. At a dose above 4 mg, PK began to report intolerable dystonia-like symptoms. Because of an absence of response to lower doses of risperidone, we believed that further escalating the dose would most likely only expose PK to side effects. As he now "failed" two antipsychotics (olanzapine and risperidone), we planned a cross-titration with clozapine.

We initiated clozapine at 25 mg for three days, then increased to 50 mg for 3 days. On day 7 we increased clozapine to 75 mg for three days and then to 100 mg. On day 13 we increased clozapine to 150 mg for three 3 days, with the plan to increase it to 200 mg on day 16. On day 15, however, PK told his mother that his chest hurt; his mother also took note of a slight fever and tachycardia. Due to concern for myocarditis, his mother immediately took PK to the emergency department. Initial laboratory work was significant for elevated troponin greater than twice the normal limit and also for elevated C-reactive protein. As this constellation of symptoms indicated myocarditis, clozapine was discontinued, and PK underwent an echocardiogram.

Fortunately, echocardiogram did not detect any abnormalities.

Our pharmacological options to treat PK's psychosis became increasingly limited. In late June 2019, we elected to use quetiapine to target schizophrenia. We favored quetiapine over aripiprazole because of the continued concern over aripiprazole's potential to cause akathisia and exacerbate excitatory catatonia. From late June to August 2019, quetiapine was titrated to a total daily dose of 800 mg. But he failed to demonstrate any response to quetiapine, either.

As treatment failures continued to accumulate, we elected to use olanzapine at treatment- refractory doses. We did not utilize this strategy earlier due because of its mixed level of evidence.

From August through October 2019, olanzapine was titrated to 40 mg nightly. His psychotic symptoms responded as the olanzapine dose was escalated beyond 20 mg, and by December 2019, his psychotic symptoms were considerably ameliorated with only mild auditory hallucinations. Catatonia remained fully resolved.

Over the following year lorazepam was slowly down titrated and discontinued without reemergence of catatonia. We attempted to reduce the olanzapine to the lowest effective dose; however, at 20 mg, psychotic symptoms began to reemerge. Olanzapine is therefore currently being continued at 25 mg nightly as maintenance treatment.

Although PK is improved, we continue to reflect on a salient and troubling issue in his care—our inability to obtain ECT. Initially, the local hospital did not pursue ECT for PK because of his lack of insurance coverage. When we approached the same hospital again regarding ECT, he was declined for the same reason. After we identified a second facility with ECT capabilities within our health system, the treatment team declined to pursue ECT. The only remaining option within our health system for ECT was outpatient ECT. However, the performing physician deemed that PK's condition was too acute for outpatient ECT. At that point, we discussed with PK's mother the option to recontact the treatment team from the second facility, but she declined. We highlight that improved access to ECT may have expedited PK's recovery.*

QUESTIONS TO THE CONSULTANTS

- How do you think about "treatment resistance" when applied to individuals with schizophrenia? (Dr. Cotes)
- How would you contextualize this young man's antipsychotic "treatment resistance" within the existing literature on this topic? (Dr. Cotes)
- For this young man, a retrial of high-dose olanzapine was chosen after he suffered clozapine-induced myocarditis. How do you approach treatment resistance, including in a patient with clozapine-induced myocarditis? What options would you consider for this patient? (Dr. Cotes)
- What is the best pharmacological approach for patients with concurrent catatonia and psychosis? (Dr. Beach)
- When would you consider ECT? (Dr. Beach)
- What would you recommend in managing the young man in this presentation regarding these concurrent problems? What patient factors would you consider most relevant in developing a treatment plan and appropriate treatment setting? (Dr. Beach)

Robert Cotes, MD

HOW DO YOU THINK ABOUT "TREATMENT RESISTANCE" WHEN APPLIED TO INDIVIDUALS WITH SCHIZOPHRENIA? The term *treatment resistance* can erroneously evoke a sense of therapeutic nihilism or can mistakenly imply that a person is "resistant" or unwilling to participate in treatment. Despite the potentially misleading nomenclature, treatment-resistant schizophrenia (TRS) is a valuable clinical and research construct that can be utilized, in part, to determine who may benefit from a clozapine trial. The incidence of TRS varies depending on the population studied and the definition used, but it is commonly cited that 20%–30% of people with schizophrenia have TRS.[1] That number may actually be higher. In a meta-analysis including over 6000 patients looking at various cutoff points with the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS), the nonresponse rate for treatment with a single non-clozapine antipsychotic was 19.8% for ≤0% change in PANSS/BPRS score, 43% for <25% change in PANSS/BPRS score, and 67% for <50% change in PANSS/BPRS score.[2] After years of various definitions applied in the literature, the Treatment Response and Resistance in Psychosis (TRRIP) Working Group published a consensus definition for TRS in 2017. Highlights of the minimum TRRIP TRS requirement include moderate clinical and functional symptoms as measured by a standardized rating scale, ≥12 weeks total duration of impairment, and ≥2 past adequate antipsychotic trials at a therapeutic dosage where a person has been adherent for at least six weeks.[3]

Clozapine is the only medication that is Food and Drug Administration–approved for TRS, and the recently published American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia recommend that patients with TRS be treated with clozapine.[4] Response rates for people with TRS are 0% for typical antipsychotics, 10% for atypical antipsychotics, and 40%–60% for clozapine.[5,6] Clozapine is generally underutilized in the United States, and there is ample evidence of racial and ethnic disparities in clozapine-prescribing practices.[7,8] Prescriber reluctance is a major barrier to clozapine's use. In a survey of 143 U.S. psychiatrists, 38% would rather combine two antipsychotics than use clozapine, and only 45% would use clozapine after two or fewer antipsychotic failures.[9] Efforts should be made to promote clozapine use as soon as possible without unnecessary antipsychotic trials. In a survey of 86 individuals on clozapine in the southeastern United States, the median number of self-reported antipsychotic trials prior to clozapine was four.[10] Some data suggest pursuing a trial of clozapine after failure of only one antipsychotic medication.[11] Delays in initiating clozapine use can result in poorer response,[12] and prescribers should make every possible attempt to reduce the duration of treatment resistance.[13]

It is important to differentiate TRS from pseudo-resistance, where the treatment is inadequate due to an incorrect diagnosis, kinetic issues, medication nonadherence, or confounding psychiatric or medical comorbidities.[14] Remembering the 5 Cs for TRS may be helpful: (1) *c*orrect diagnosis, (2) addressing *c*omorbid conditions, (3) assessing *c*ompliance, (4) obtaining *c*oncentrations of antipsychotics, and (5) understanding *c*ontinuous psychosocial stressors.[15] For many individuals, TRS may be

* The case history was prepared by Mohan Gautam, DO, MS, and Mauran Sivananthan, DO.

present from the initial onset of psychosis, but for some, it may develop later in the illness.[16]

The pathophysiology of schizophrenia, in general, and the pathophysiology of TRS, in particular, are not completely understood. Although biological differences may exist between people with TRS and people with treatment-responsive schizophrenia, no biomarkers, to date, are clinically available that allow clinicians to predict who is a clozapine candidate.[17] Current biological hypotheses about TRS include dopamine suprasensitivity, glutamate dysregulation, inflammation and oxidative stress, and hyperdopaminergic and normodopaminergic subtypes.[18] Complicating the matter is a degree of both biological and clinical heterogeneity within schizophrenia that likely extends to TRS.[19]

How would you contextualize this young man's antipsychotic "treatment resistance" within the existing literature on this topic? Prior to the clozapine trial, the patient was exposed to two different antipsychotics on three separate occasions: (1) risperidone 0.5 mg twice per day, discontinued due to potentially worsening catatonia, (2) olanzapine titrated to 20 mg, six weeks in duration, discontinued due to lack of efficacy, and (3) retrial of risperidone, titrated to 4 mg, three months in duration, which was discontinued due to dystonia. Obtaining therapeutic drug monitoring may be useful before an antipsychotic trial is deemed a failure—specifically for olanzapine in this situation. Jointly, the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie "strongly recommends" the use of therapeutic drug monitoring for olanzapine (therapeutic blood level range, 20–80 ng/mL) for a variety of situations, including when usual therapeutic doses fail to produce a clinical response.[20] Additionally, for this patient, his smoking status was unknown. Aryl hydrocarbons produced from cigarette smoking are strong inducers of CYP1A2 and can lead to clinically relevant decreases in olanzapine levels.[21]

Psychiatric and medical comorbidities are more common among individuals with TRS than in those without TRS.[22] The diagnoses of both autism spectrum disorder (ASD) and catatonia can certainly complicate and delay the diagnosis of TRS. The prevalence of ASD in individuals diagnosed with psychosis exceeds what would be expected in the general population.[23] Evidence, though limited, suggests individuals with ASD who do not respond to other antipsychotics for disruptive behavior may benefit from a clozapine trial.[24] The ongoing symptoms of catatonia likely narrowed the list of available antipsychotic medications and, in many scenarios, could lead to a delayed diagnosis. Regarding catatonia, clinicians would think of mood disorders perhaps being more common causes of catatonia than psychotic disorders. However, catatonia can be a feature of schizophrenia without a misdiagnosis. In a meta-analysis examining the prevalence of catatonia, 33 studies found the prevalence of catatonia among individuals diagnosed with schizophrenia to be 9.8%.[25]

For this young man, a retrial of high-dose olanzapine was chosen after he suffered clozapine-induced myocarditis. How do you approach treatment resistance, including in a patient with clozapine-induced myocarditis? What options would you consider for this patient? The patient's treatment team should be commended for pursing a trial of clozapine when they did, but unfortunately, the patient developed symptoms concerning for clozapine-induced myocarditis (CIM). This potentially life-threatening, adverse effect of clozapine has received increased attention in recent years. A systematic review and meta-analysis found that 6 per 1000 people exposed to clozapine developed CIM, with rates higher in Australia.[26] However, a recent U.S. study (with a smaller sample size) found rates of presumptive myocarditis in 5.3% of first-time starts on clozapine.[27] The mean time until onset for myocarditis due to clozapine is 17 days, with 82% occurring between days 14 and 21.[28] Risk factors for CIM include older age, co-prescription of sodium valproate, and possibly more rapid clozapine titrations.[29]

Ronaldson and colleagues[28] have proposed a myocarditis screening protocol that includes baseline echocardiogram, troponin I/T, and C-reactive protein (CRP). Troponin I/T and CRP are repeated on days 7, 14, 21, and 28 of treatment. Elevation of troponin beyond twice the upper limit of normal or CRP elevation above 100 mg/L is sensitive and specific for myocarditis, and the authors recommend stopping clozapine. Myocarditis screening protocols are typically used for the first six to eight weeks after clozapine initiation, and baseline echocardiograms are uncommon in the United States. Currently, the American Psychiatric Association schizophrenia guidelines do not call for mandatory screening labs for clozapine-induced myocarditis,[4] but this practice has been more common clinically. Cardiac MRI, showing edema and late gadolinium enhancement, is often one of the best tests to evaluate for clozapine-induced myocarditis,[30] but the investigation was not conducted in this case and can be difficult to obtain in the acute setting.

For patients who have developed CIM, the therapeutic options are often limited. Prior antipsychotic trials should be reviewed to determine what, if any effect, the other medications have had. Other non-clozapine antipsychotics are often unlikely to be helpful if the patient does have TRS. Although several studies have reported the successful use of high-dose olanzapine (>20 mg/day) for TRS,[31,32] this strategy is generally inferior to clozapine when the two are specifically compared.[33] PK, the patient in the present case, was fortunate to have a response to high-dose olanzapine. Additionally, details around the myocarditis should be reviewed to determine how convincing the case of myocarditis was. Per the Ronaldson protocol,[28] troponin elevation twice the upper limit of normal is sufficient, but there are other causes of elevated troponin, such as physical exercise, which generally peaks after the first four hours.[34,35] In this case, the magnitude of the CRP increase was not quantified; it was noted only to be elevated.

A known history of CIM is not an absolute contraindication to rechallenge with clozapine, and can be pursued with

caution, monitoring, and a detailed risk/benefit conversation with the patient (and support system, if applicable). In a review of published case reports, rechallenge after myocarditis was successful in 11/17 cases.[36] Some keys to successful re-titration potentially include a very slow titration, careful (and possibly daily) vital sign monitoring, and co-management with cardiology. Some authors recommend delaying a clozapine retrial until six months after the initial CIM episode.[37]

Scott Beach, MD

WHAT IS THE BEST PHARMACOLOGICAL APPROACH FOR PATIENTS WITH CONCURRENT CATATONIA AND PSYCHOSIS? Catatonia is best thought of as a syndrome—a constellation of symptoms that, like delirium, can occur in the setting of various psychiatric and neuromedical insults, particularly in patients with a preexisting vulnerability. Regardless of the underlying diagnosis, catatonia often occurs in the presence of psychosis. The psychosis may exist as a symptom of a psychiatric illness such as schizophrenia, bipolar disorder, or unipolar depression, or it may occur in the setting of delirium or substance use. Common psychotic experiences in catatonia include persecutory and nihilistic delusions. Cotard's syndrome, for example, in which patients believe that they are dead or dying, rotting from the inside, or missing vital organs, has a high overlap with catatonia. Following an episode of catatonia, many patients will have psychotic explanations for some of their catatonic features. For example, they may state that the voice of Satan was telling them not to move or speak, or that they felt as though they were being controlled by some outside force and did not have control over their limbs.

Despite the common overlap, the management of co-occurring psychosis and catatonia represents a major treatment challenge. One of the guiding principles of managing catatonia is that, as with delirium, the underlying cause must be treated in order to prevent recurrence. It is therefore essential to consider the context in which catatonia is occurring when choosing a treatment approach. Other important factors to consider include potential medical comorbidities that may convey risk with certain management strategies, the duration of catatonia (with longer durations typically conveying a lower treatment response), the presence of malignant features, prior medications trials and past responses, and the current setting.

As the first-line treatment for catatonia, benzodiazepines are unlikely to mitigate psychosis and may, in fact, unmask psychosis by temporarily treating the catatonia. It is not uncommon, for example, for an immobile, mute patient with catatonia to suddenly become aggressive and with obvious psychosis following a lorazepam challenge. Similarly, amantadine, which is sometimes used as a second- or third-line agent in managing catatonia, has dopamine agonist properties, which can directly worsen psychosis. Conversely, antipsychotic agents have the potential to induce or worsen catatonia, sometimes leading to the development of malignant features, including fever, autonomic instability, and lead-pipe rigidity, and must therefore be used very cautiously in catatonia.

In approaching the management of a patient with catatonia and psychosis, although benzodiazepines have the potential to unmask psychosis, they still represent the best initial course of action. Benzodiazepines are thought to work by causing a reduction in orbitofrontal cortex and ventromedial prefrontal cortex hyperactivation, leading to a regularization of the orbitofrontal cortex activity, as well as GABA-A interneuron agonism in the striatum, ventral tegmental area/substantia nigra, and thalamus.[38] Lorazepam is the preferred benzodiazepine because of its preference for GABA-A receptors, combined with its availability in a variety of preparations.[39] Generally, a 2 mg lorazepam challenge is used to confirm the diagnosis of catatonia and assess the likely response to benzodiazepines. For patients in hospital settings, intravenous lorazepam is always preferred, as it is fast acting and, despite having the same $T_{1/2}$ as other forms, has a longer effective length of action. Intramuscular preparations are generally avoided for repeat injections, as they may worsen the catatonia fear response and may also create challenges in determining whether malignant features are present by elevating the creatinine kinase. On an outpatient basis, sublingual lorazepam is preferred over the oral form, as it appears to have greater effect. Dosing of lorazepam is typically started at 2 mg every 6–8 hours, though higher doses up to 24 mg daily are sometimes needed. Importantly, lorazepam may need to be dosed more frequently in patients with refractory catatonia and ideally should be dosed around the clock in order to prevent worsening overnight in the setting of a long interval between doses. Benzodiazepines should not be held for sedation in the setting of catatonia.

WHEN WOULD YOU CONSIDER ECT? When psychosis is present, attempts should be made to pursue electroconvulsive therapy as early as possible. Some evidence suggests that benzodiazepines may be less effective for catatonia in the setting of psychosis, particularly if the psychosis is the result of an underlying schizophrenia spectrum disorder, though this teaching has been called into question in recent years.[40] Guidelines regarding ECT vary significantly by state, and ECT may not be a feasible strategy in many jurisdictions. In some states, a court order is required, which can be a prolonged process. Depending on the presence of medical comorbidities, individual ECT services may also be reluctant to pursue treatment of specific patients. Nonetheless, ECT represents the best chance for improvement in comorbid catatonia and psychosis, with improvements seen in up to 90% of patients, including up to 60% of those who fail benzodiazepines.[41] The exact mechanism of ECT in catatonia remains unclear, but possible effects include increased blood flow to orbitofrontal and parietal cortices, increased GABA activity and GABA receptor expression, increased dopamine release and modulation of dopamine receptors, and possible immunomodulatory effects.[42]

If ECT is an option, consent must be obtained. Since most catatonic patients will be unable to give consent for the procedure, a proxy consent is typically used. Typically, at least 6 sessions of ECT are required to treat catatonia, with most patients requiring 9–12 sessions. Bitemporal placement with brief pulse is most commonly used, and patients are typically treated at least three times weekly and sometimes daily. Some evidence suggests that a combination of ECT and low-dose lorazepam may be particularly efficacious.[43] If the ongoing use of lorazepam presents concerns about the seizure threshold, flumazenil and augmentation with hyperventilation and caffeine can be considered. For patients who improve with ECT, maintenance treatments are often required to prevent relapse.

WHAT WOULD YOU RECOMMEND IN MANAGING THE YOUNG MAN IN THIS PRESENTATION REGARDING THESE CONCURRENT PROBLEMS? WHAT PATIENT FACTORS WOULD YOU CONSIDER MOST RELEVANT IN DEVELOPING A TREATMENT PLAN AND DETERMINING AN APPROPRIATE TREATMENT SETTING? In this case, I would want to understand better what the ECT physician felt were the significant risks associated with treatment. If these risks could be mitigated in some way, ECT has the potential to be a life-altering treatment for this patient.

If the catatonia does not respond to benzodiazepines and ECT is not an option, several other medications have been used for catatonia. NMDA antagonists such as memantine and amantadine would typically be the next step in the treatment algorithm, though they would not specifically target the underlying psychosis.[44] Another option would be to use an antiepileptic drug, such as valproate or carbamazepine. This option may be a particularly attractive if the catatonia and psychosis are thought to be secondary to an underlying bipolar disorder.

As in this case, antipsychotic agents are often considered for the management of co-occurring catatonia and psychosis. Case reports of success in treating catatonia exist for many second-generation antipsychotics.[45] Atypical antipsychotics are hypothesized to treat catatonia via effects on serotonin receptors, which may lead to an increase in dopamine in the prefrontal cortex.[46] In general, we recommend using low-potency agents to minimize the risk of worsening catatonia or inducing a malignant catatonia. Additionally, antipsychotics should always be given directly in combination with benzodiazepines in order to further minimize the risk.

Risperidone has been reported to have been successful in treating seven cases of catatonia, almost all of whom had an underlying schizophrenia.[44] As a high-potency agent, however, it may not be the ideal first choice for an antipsychotic and should be used with extreme caution—and always combined directly with benzodiazepines. In this case, the case history posits that risperidone may have led to worsening of catatonia when it was first used. Clozapine has been used in a handful of cases but seems to be most effective when catatonia occurs in the setting of clozapine withdrawal. In this case, clozapine had to be stopped because of the development of myocarditis. Interestingly, quetiapine has never been successfully used to treat catatonia in any reports—which would be consistent with what happened in this case. Olanzapine has also been reported as successful in seven cases and may be a better option, given its relatively lower potency.[44] In this case, the patient's catatonia appears to have eventually responded well to high-dose olanzapine, which also successfully treated his psychosis.

Of all of the antipsychotics, aripiprazole has actually been reported to have been successful in the largest number of cases (9) and may be a great choice because of its partial-agonist activity at the D2 receptor, which may lower the risk of worsening catatonia.[7] While the concern about inducing akathisia is certainly valid, the potential benefits of aripiprazole over other antipsychotic agents may outweigh this risk. Furthermore, aripiprazole has a relatively wide dose range, which may be advantageous if high doses are needed.

FINAL QUESTIONS: How would you manage this young man going forward? Do you recommend certain monitoring parameters or referrals? Do you foresee the development of other complications? (Drs. Beach and Cotes)

Scott Beach, MD

The patient's catatonia has remained in remission following successful treatment. Given the severity and the duration of the catatonia, PK is definitely someone for whom I would consider maintenance benzodiazepine treatment as a way to mitigate the risk of recurrence. While no guidelines exist for maintenance therapy, it is an important consideration in patients who have prolonged episodes of catatonia that are refractory to treatment. Two of the biggest risk factors for catatonia recurrence are the rapid taper of benzodiazepines and repeated episodes of catatonia, neither of which applies in this case. Nonetheless, the patient's catatonia was clearly refractory to multiple treatments, and his psychotic disorder appears to be fairly brittle—both of which may increase the risk for recurrence. Furthermore, his underlying autism spectrum disorder conveys a high-risk for catatonia, with many patients experiencing recurrent episodes of catatonia throughout their lives. Given these factors, PK may be someone who would benefit from continued treatment with lorazepam 1–2 mg daily. While some prescribers worry about the risk of long-term benzodiazepine usage, including dependence and cognitive concerns, most patients treated with maintenance benzodiazepines for catatonia do not develop significant problems. It is also worth noting that subsequent episodes of catatonia may prove even more challenging to treat, making a more compelling argument for prevention. It is even possible that catatonia, like epilepsy and mood disorders, could create a kindling effect, whereby each subsequent episode increases the risk of further future episodes and the interval in between episodes becomes shorter. The typical course of periodic or recurrent idiopathic catatonia would seem to fit such a hypothesis.[46,47]

In terms of the antipsychotic medication, olanzapine appears to be a successful strategy for mitigating his psychosis and should be continued. The case points out that an attempt to taper the dose even slightly led to reemergence of psychosis. As noted above, the fact that olanzapine is a low-potency agent means that it conveys lower risk for worsening catatonia than some other agents may. Were olanzapine to cease being effective at some point, or intolerable side effects to develop, it would be worth reconsidering a trial of aripiprazole, given the advantages outlined above.

The Bush-Francis Catatonia Rating Scale is an excellent tool for monitoring for reemergence of catatonia and should be administered at regular intervals during psychiatric follow-up. Given that patients with recurrent catatonia most commonly display the same symptoms with each episode, it would be reasonable to pay particular attention to early symptoms such as mutism, withdrawal, and immobility in PK's case. Psychiatrists should keep in mind that all of the symptoms of catatonia exist on a spectrum; presentations may be quite subtle early on. For example, whereas many psychiatrists think of mutism only as a marked reduction in, or the complete absence of, speech, other forms of mutism include hypophonia, reduced speech, and unusual speech patterns such as one where the volume of the voice decreases toward the end of each sentence or clause. Should symptoms reemerge, early treatment with benzodiazepines may be useful in mitigating symptoms. Sublingual, rather than oral, lorazepam may be helpful if available, and outpatient treaters might consider an increased frequency of dosing, such as every six hours if needed.

Should PK become catatonic again, it will be important to monitor him for complications, particularly if his catatonia is prolonged, as it was during his first episode. Simple catatonia can lead to a host of medical sequelae, including aspiration, dehydration, pneumonia, deep vein thrombosis, pulmonary emboli, and urinary retention. Were PK to develop malignant features of catatonia, potential sequelae include acute renal failure, acute respiratory distress syndrome, cardiac arrest, disseminated intravascular coagulation, seizures, rhabdomyolysis, respiratory arrest, and death.

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I would be curious to learn more information about the nature of the current reemergence of symptoms and the level of functional impairment. I would also be interested to learn what is most bothersome for the patient and to develop the treatment plan around his priorities. It would be helpful to quantify and track symptoms with a brief rating scale, like the Clinician-Rated Dimensions of Psychosis Symptom Severity scale found in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[48] or the Clinical Global Impression Scale.[49] Ongoing monitoring for catatonia with the Bush-Francis Catatonia Rating Scale would also be warranted. I would have a low threshold to restart lorazepam should the symptoms of catatonia appear again.

Having the patient remain on olanzapine and titrating the dose to symptom improvement in the short-term is a reasonable strategy. However, olanzapine has one of the most significant cardiometabolic liabilities of any antipsychotic,[50] and the effect may be more pronounced in young people.[51] It would be essential to monitor for weight gain, diabetes, and hyperlipidemia per the American Psychiatric Association/American Diabetes Association Consensus guidelines.[52] In addition to counseling about diet and exercise, augmentation with a compound that might help to mitigate weight gain, such as metformin, may be a consideration. In a meta-analysis including four studies and 105 patients on olanzapine and metformin (doses ranging from 750–1750 mg), the weighted mean difference for body weight was 5 kg lower for metformin versus placebo.[53] If the positive symptoms remain problematic and functionally impairing, a rechallenge with clozapine is a possibility even after myocarditis, but the same cardiometabolic issues remain.

Consideration of aripiprazole, which would have a more benign cardiometabolic profile,[50] may be an option rather than olanzapine. Available evidence suggests that switching to aripiprazole from other antipsychotics is feasible from an efficacy standpoint and may reduce cardiometabolic burden.[54] In a meta-analysis looking at 22 randomized, controlled trials, no difference in psychotic worsening was found when switching to aripiprazole versus switching to another antipsychotic, although switching to aripiprazole was associated with greater risk of study discontinuation because of the lack of efficacy.[55] In a population-based cohort study from the United Kingdom that involved 1643 people starting aripiprazole who had previously been taking another antipsychotic, the treatment failure incident rate was 13.1 per 100 person-years, which did not differ significantly from those who were switched to a different antipsychotic.[56] Taken together, these studies suggest that transition to aripiprazole is possible but that clinical vigilance is necessary. Furthermore, in a patient with a recent history of catatonia, aripiprazole may be a reasonable option and may be less likely than other high-potency antipsychotic agents to worsen catatonia.[44]

Finally, I would make sure to optimize psychosocial interventions, which could include cognitive-behavioral therapy for psychosis, supported employment, peer support, and family-based interventions. With symptoms beginning in January 2019, the patient may, in some areas, still be eligible for coordinated specialty care services for first-episode psychosis, which has been shown to improve outcomes in multiple domains.[57,58]

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