Positive Response to Ketamine Administration in Treatment Resistant Psychosis: A Case Report

Joseph Pullara, M.D.

Abstract:
The pathophysiology underlying the schizophrenia spectrum of disorders has been a topic of research for decades. Ketamine has been used as a model for psychosis for over 20 years [1]. Treatment of refractory cases of schizophrenia and similar disorders remains a challenging aspect of psychiatry. This case report describes the case of a 45-year-old woman with treatment refractory schizoaffective disorder who was transitioned off of clozapine due to neutropenia. This resulted in psychotic destabilization and a complicated clinical course, ultimately resulting in a re-trial of clozapine after the failure of alternative psychotropic treatment. During this trial, an MRI brain was obtained, which required a sedating dose of intravenous ketamine due to patient agitation. After just a single dose of ketamine, resolution of behavioral activation and agitation was noted for a short period, something which had not been seen in over a month of hospitalization.

Introduction

Schizoaffective disorder is a psychiatric illness that results in both psychotic and affective symptomatology, initially described as a subtype of schizophrenia that became a standalone diagnosis in later editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Treatment commonly consists of multiple psychotropic medications to treat symptoms of psychosis, depression, mania, or a combination of symptoms [2]. When psychosis persists despite trials of multiple antipsychotic medications, clinicians start to have discussions with patients and their families about the use of clozapine. If clozapine fails to resolve symptoms or if patients are required to discontinue treatment due to harmful adverse reactions (i.e. neutropenia, clozapine-induced myocarditis, or bowel obstruction due to constipation), clinicians face the difficult decision of which treatment direction to proceed next.

Case Report

Mrs. K was a 45-year-old Asian female with a history of schizoaffective disorder, bipolar type who was involuntarily admitted to a state psychiatric facility after displaying delusional religiosity and agitation during a mental health screening at a community mental health center. The patient was an Asian immigrant who had moved to the United States at age 5. She had struggled with schizoaffective disorder for the majority of her adult life but had previously been psychiatrically stable on clozapine. Unfortunately, one month before admission, the patient's absolute neutrophil count (ANC) decreased to 820mm^3. Given this, the decision was made to taper off of Clozapine and onto olanzapine due to its psychopharmacologic similarities.

On admission, it was unclear whether she had been taking any oral medications at all. During the intake process, she was threatening both peers and staff and attempting to elope. The patient believed that her mother lied to her about her father's death in the Vietnam war and that he was still alive and had visited her. Providers attempted to treat this mood lability and psychosis with various mood stabilizers & antipsychotics, but the patient continued to refuse oral medications. Due to concerns for her safety and the safety of other patients, the decision was made to institute a medication over rejection order, and she was given intramuscular (IM) psychotropic medication each time she refused the oral formulations of medications. Despite receiving numerous doses of IM fluphenazine, chlorpromazine, olanzapine, diphenhydramine, and

lorazepam throughout the first week of admission, the patient's condition did not improve. The patient remained aggressive towards staff & other patients, displayed self-harming behaviors, refused most oral nutritional intake, and slept less than 3 hours each night of this hospitalization. On one occasion, the patient was seen banging her head on a wall aggressively, despite one-to-one monitors attempting to prevent her from doing so. Given signs of volume depletion and concern for a head injury, the patient was transferred to a local emergency room for imaging and medical workup.

Three weeks later, the patient was deemed medically stable and was transported back to the state psychiatric facility. The patient had been treated for volume depletion and completed a course of antibiotics for a urinary tract infection. Providers had tried to rechallenge the patient with clozapine during her three-week admission at their facility, but the patient again refused most oral medications. When the patient arrived back at the state psychiatric facility for this second admission, she believed that she was God and had been communicating with the devil. The patient was again refusing oral medications and most attempts at oral nutritional intake. The patient's behaviors resulted in many hours of seclusion and physical restraints over the majority of her hospitalization. Even with continuous one-to-one monitoring by staff, the patient remained labile, aggressive towards other patients, sexually inappropriate with staff and other patients, and displayed various forms of self-harming behaviors ranging from slamming her hands onto doors to hitting her head on walls.

Providers tried to reinforce the importance of oral medications continually, but the patient was unable to display any insight into her condition. Throughout what would eventually lead to a three-month admission, she was trialed on combinations of scheduled intramuscular fluphenazine, chlorpromazine, ziprasidone, olanzapine, and haloperidol. Electroconvulsive therapy was considered but providers did not feel the patient was a candidate for this treatment modality, nor would she have been able to give informed consent to treatment. Almost a month into the patient's admission, providers began another trial of clozapine but the patient continued to refuse oral medications intermittently.

One morning, after an overnight incident in which the patient purposefully hit her head on a wall forcefully, the decision was made to transfer the patient to a nearby medical facility for head imaging. At that facility, emergency room physicians decided to perform magnetic resonance imaging (MRI) of her brain. Before the procedure, the patient displayed continued agitation and aggression, so the decision was made to provide adequate sedation in the form of intravenous ketamine. Results of the MRI were unremarkable for acute or chronic pathology, but the patient's mental status and affect were notably different.

Upon awakening from the procedure, the patient was transferred back to the state psychiatric facility. When the patient arrived, she began apologizing to staff for her behavior over the previous few months. The patient expressed interest in seeing her husband again, something she had not mentioned during her entire admission. She was agreeable to taking oral medications; in particular, the patient recalled how important clozapine had been in her life before admission. The patient's sleep patterns remained irregular but had overall improved significantly. The patient remained agitated at times, but much less than previous and could be adequately monitored with 15-minute checks for safety instead of continuous one-to-one monitoring. One week after returning from MRI, the patient was discharged to home care with her husband and mother-in-law. The family considered her recovery to be a "miracle." Ultimately, she was discharged on a combination of clozapine 900mg daily (in divided doses), quetiapine 400mg nightly, and ziprasidone 120mg twice daily.

Before discharge, providers attempted to establish the patient with outpatient services at local ketamine clinics, both with intravenous ketamine and intranasal Spravato (esketamine) but were unable to do so because of financial concerns and lack of insurance coverage. After coordinating care with outpatient providers, the plan was to continue oral antipsychotics and eventually try to taper down to two antipsychotic medications instead of three,

due to the well-known dangers of combining multiple antipsychotic medications. Unfortunately, the patient decompensated and was readmitted involuntarily to the state hospital for a third time just three months after her second admission. She presented with similar agitation and delusional religiosity. She believed that she was pregnant with the son of Jesus, that she was a famous movie star, and that President Jimmy Carter was the leader of the entire world. This admission was similar to previous admissions with much time spent in the seclusion room and requiring physical restraints. After three weeks, she was found to be stable enough to transfer from the acute psychiatric unit to a long-term state psychiatric facility, where she currently resides at the time of publication. Providers were not able to get the state hospital to approve the use of intranasal esketamine or intravenous ketamine.

Discussion:

Ketamine is a widely used pharmacologic agent first synthesized in 1962 as an analog of the anesthetic phencyclidine [4]. It was first used in psychiatry as a drug model for psychosis but later found to be therapeutic for patients with refractory depression [1]. Its use in the intravascular formulation has never been approved by the Food and Drug Administration (FDA) to treat depression, but its use in private practice ketamine clinics is not uncommon across the United States. When used in a sub-anesthetic context, its effects on depression and suicidality have shown positive results in some clinical trials. In March of 2019, the FDA approved the use of intranasal Spravato (esketamine), the S(+) enantiomer of ketamine, for use in adult patients with treatment-resistant depression without psychotic features [5]. While studying esketamine in clinical trials, a critical exclusionary criterion is having a history of a psychotic disorder (including major depressive disorder with psychotic symptoms) or a history of bipolar disorder as researchers have known for almost 20 years that subanesthetic doses of ketamine can induce psychosis similar to that seen in schizophrenia[1,3].

While reviewing the case described above, one would naturally question why ketamine was chosen for sedation in this patient's case given her long history of psychosis. Unfortunately, this was not documented in the records available for review. One hypothesis for why ketamine was helpful in this case without exacerbating psychosis is that this patient had been taking oral clozapine at the time of IV ketamine administration. Granted, the patient had been skipping doses intermittently in the weeks leading up to the MRI, but there is literature to suggest that clozapine has a unique NMDA receptor effect and can blunt the psychotic effects of ketamine in patients with schizophrenia and schizoaffective disorder [6]. How this patient would have responded to intranasal esketamine or repeat infusions of subanesthetic doses of IV ketamine will never be known but may reveal itself as an area for further study in the future.

AUTHOR INFORMATION:

Send correspondence to Dr. Joseph Pullara (jpullara@kumc.edu)

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