A Review of Current Strategies in Treatment-Resistant Schizophrenia: Considering Paliperidone Palmitate LAI With and Without Olanzapine as an Alternative to Clozapine

Raghav Malik, MD and Muhammad Zaidi, MD

DC Department of Behavioral Health, Washington, DC, USA

Abstract

Background. Schizophrenia is a debilitating mental illness that affects patient's function and quality of life. Estimates indicate a lifetime prevalence of 0.48%, causing up to 13.4 million years of life burdened by disability. 30% of these patients are deemed as having treatment-resident schizophrenia (TRS), a subset of which do not respond to clozapine, the medication designated for TRS. Those that do not respond to clozapine are deemed to have clozapine-resistant schizophrenia (CRS), requiring further augmentation or multiple antipsychotics.

Current limitations. Clozapine only has limited formulations available (oral [PO] and dissolving [ODT]) and has a substantial side effect burden. Most serious among these side effects includes agranulocytosis, which in some cases can cause severe infections such as septicemia. Regular blood draws monitoring for this are vital to prevent this dangerous consequence, but place further burden on patients, requiring weekly to monthly lab work and visits. Other common and burdensome side effects include tachycardia, hypotension, sialorrhea, weight gain, and metabolic syndrome, to name a few. However, treatment for TRS is still needed, and further alternatives must be explored.

Proposed alternatives. Among studies done on clozapine, few compare second-generation antipsychotics head-to-head, and those that do find similar improvement in overall symptom burden among multiple antipsychotics, especially olanzapine and paliperidone (in particular, paliperidone palmitate). Due in part to the improved receptor profile of these medications (especially 5-HT2A, 6, and 7) compared to clozapine, they can have similar or superior effect in patients with TRS without substantial patient side effect and functional burden. Paliperidone palmitate formulations are developing that can be spaced further and further apart, allowing for minimal impact on patient's livelihood, while demonstrating similar overall effect with improved side effect profile. However, onset of action is slow, and an effective adjunct strategy may be to initially administer olanzapine for the first 6 months until peak effect is expected from paliperidone palmitate, at which point monotherapy with paliperidone is preferred.

Conclusions. Alternative therapies for patients with TRS may be more functional with fewer side effects, and this work indicates a particularly effective strategy may be to pursue paliperidone palmitate monotherapy long-term while utilizing the unique combination of paliperidone and olanzapine in the short-term (first 6 months) while awaiting peak efficacy.

Funding. No Funding

Ketamine in the Treatment of Delusions: A Review of the Evidence

Renzo Costa, MD[1], John Guieb, MS3[2], Ayyub Imtiaz, MD[1] and Muhammad Zaidi, MD[1]

[1]Saint Elizabeth's Hospital, Department of Behavioral Health, Washington, DC, USA and [2]George Washington University School of Medicine, Washington, DC, USA

Abstract

Introduction. Delusions are defined as fixed false beliefs that are not within normal parameters of society, culture, or religion that can be part of psychotic or mood disorders. They can be difficult to treat and, for some inpatient individuals, persistent delusions can make safe discharge impossible. Ketamine is a dissociative agent that has shown promise in treating mood disorders. Despite this, clinicians hesitate to prescribe this when a patient presents with any type of psychotic symptom. There is proof that ketamine is safe to use with psychotic symptoms, and there is growing evidence that it may be a suitable treatment alternative for delusions resistant to other psychopharmacology.

Methods. A literature review using articles from multiple databases was conducted to gather supporting evidence on the use of ketamine in the context of psychosis. Since there has not been a reported conducted study specifically for ketamine and delusions, a look into its use for psychosis was done to find links between the neurobiology of delusions and the mechanism of action of ketamine.

Results. Current literature does not demonstrate that ketamine within a therapeutic setting exacerbates psychotic symptoms in those with depression or bipolar disorder, regardless of the presence of psychotic features, nor does it reveal that predisposed patients experience lasting psychotic effects. Furthermore, although ketamine is often used to model schizophrenia, brain connectivity seen during ketamine-induced delusions is opposite to the connectivity seen in delusions in the context of chronic schizophrenia. Regardless of connectivity patterns, ketamine appears to act upon many of the same mechanisms that underlie delusions. There is evidence delusions are characterized by low belief flexibility, high prediction error, and high aberrant salience. An animal model of stress-induced cognitive dysfunction found that ketamine corrected the cognitive flexibility deficits. Ketamine has been shown to alter prediction error in those suffering from major depressive disorder, resulting in greater optimism bias when patients update maladaptive beliefs post-ketamine administration. In respect to aberrant salience, neural networks affecting this include midbrain dopaminergic neurons and their projections to striatal and frontal cortical regions. Studies have shown this effect was reduced by ketamine-induced plasticity in the orbitofrontal cortex.

Conclusion. Psychotic symptoms may not be an absolute contraindication for ketamine treatment. In fact, ketamine could be beneficial in the treatment of various mental illnesses with psychotic features that are not amenable to classical treatment. The dissociative properties may jump-start treatment while waiting for antipsychotics to work. This could significantly reduce hospital stays, especially for patients in long-term facilities.

Funding. No Funding