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Treatment of a resistant case of schizoaffective disorder with lumateperone: A case report

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Abstract

To this day, there exists skepticism about the reliability and clinical utility of the diagnostic criteria and classification of schizoaffective disorder. In addition, the treatment of schizoaffective disorder, especially of treatment-resistant cases, has been minimally investigated. As a result, formulating official treatment guidelines for schizoaffective disorder has been challenging. We present a case of a 27-year-old female, diagnosed with schizoaffective disorder, bipolar type, for whom, for over 5 years, trials of traditional treatments, to include psychotherapy, pharmacotherapy, and electroconvulsive therapy, were either partially effective or discontinued due to intolerable side effects. The subsequent off-label use of lumateperone led to an adequate response. Lumateperone is an atypical antipsychotic, approved by the Food and Drug Administration for schizophrenia and bipolar depression in adults. Interestingly, it has a similar structure and mechanism of action to paliperidone, the only Food and Drug Administration-approved medication for schizoaffective disorder. Through this case report, as an example of lumateperone's effectiveness and tolerability, as well as a literature review of its pharmacodynamics, we make the case that lumateperone emerges as a promising option for schizoaffective disorder, especially treatment-resistant cases.

Keywords

Lumateperone, schizoaffective disorder, case report

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Introduction

Schizoaffective Disorder (SAD) is a complex psychiatric condition, characterized by the concurrent presence of psychotic and mood symptoms for the majority of the illness, at least 2 weeks of psychotic symptoms in the absence of significant mood symptoms within the illness duration, and symptoms of a mood disorder for the majority of the active and residual course of illness.[1,2] It is further subcategorized into depressive and bipolar types, based on whether only depressive or also manic symptoms constitute the mood episodes, respectively.[3]

There have been ongoing discrepancies and conflicts regarding its nosological status.[4] The variability in diagnostic criteria over time, as well as the overlap with other psychiatric conditions such as schizophrenia and mood disorders, has contributed to debates about the precise conceptualization and classification of SAD.[4] Consequently, formulating specific guidelines for the pharmacotherapy of SAD has proven to be a considerable challenge.[5]

The challenges in determining appropriate pharmacotherapy are further compounded in the case of treatment-resistant SAD. To date, approaches to treatment-resistant cases of SAD have focused on electroconvulsive therapy (ECT)[6] and clozapine.[7]

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Table 1. Medication history.

Medications used	Max daily dose used (mg)	Duration of usage	Reason for stopping
Paliperidone	6	-10 weeks (12/16–3/17	SE; drooling and spacing out
Paliperidone	234	-12 weeks (12/16–3/17)	Breakthrough episode
Palmitate LAI		-28 weeks (10/19–6/20)	Breakthrough episode + SE; excessive persistent fatigue and weight gain
Risperidone	4	-6 weeks (3/17–5/17) -36 weeks (5/17–3/18)	SE; excessive fatigue, daytime sleepiness, lack of focus, increased appetite, swelling in feet
Bupropion	200	-24 weeks (9/17–3/18)	Noncompliance
Oxcarbazepine	1200	-25 weeks – 600 mg (11/19–5/20) -26 weeks – 900 mg (6/20–1/21) -8 weeks – 1200 mg (1/22–3/22)	Breakthrough episode/ Noncompliance
Quetiapine	800	-32 weeks –100 mg (6/20–2/21) -4 weeks – 800 mg (8/21–9/21)	Persistent significant fatigue and intolerable weight gain
Aripiprazole IM LAI	400	-11 weeks (10/21–1/22)	Breakthrough episodes (twice)
Haloperidol	20	-13 weeks (1/22–4/22)	SE; Tremors, Cogwheel rigidity
Divalproex sodium	1500	-20 weeks –750 mg (12/16–5/17) -32 weeks – 500 mg (5/17–1/18)	SE; daytime drowsiness, pedal edema

LAI: Long Acting Injectable; MAX: Maximum; mg: milligram; SE: Side Effects.

Lumateperone is a second-generation antipsychotic (SGA) that has been approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia[8] and bipolar depression in adults.[9] Lumateperone's modulation of serotonin (5-HT), dopamine (D), and glutamate neurotransmission offers a unique pharmacological perspective for managing diverse neuropsychiatric disorders, including SAD.[5,10] Furthermore, it has also been demonstrated to not cause significant motor, cardiometabolic, and endocrine adverse effects.[11]

In this case report, we present the case of a 27-year-old female diagnosed with SAD, bipolar type, whose psychotic and mood symptoms did not adequately respond to the extensive combinations of various traditional treatment modalities over a period of 5 years. The patient eventually exhibited an adequate response to lumateperone, suggesting the potential efficacy of this novel medication for treatment-resistant SAD and warranting the design and conduction of experimental studies investigating this medication for both the nontreatment-resistant and treatment-resistant cases of SAD.

Case report

Patient J is a 27-year-old married female with a 6-year history of SAD, bipolar type. Her initial evaluation was in February 2016, at an outpatient clinic at 22 years of age, 2.5 months postpartum. In the 2 months prior to this visit, she had been hospitalized 3 times for acute psychotic episodes with hallucinations and delusions with sexual themes and religious preoccupation, disorganized behavior, and negative symptoms to include social withdrawal, anhedonia, and excessive guilt. The patient had been discharged with the differential diagnosis of postpartum psychosis, major depressive disorder with psychotic features (postpartum onset) and schizophrenia after ruling out organic causes via imaging and lab tests and drug-induced psychosis via a urine drug test. As per husband and patient, these episodes started after the birth of their child. There was no prior history of psychiatric illness. At the outpatient clinic, the patient was encouraged to continue the medications prescribed upon discharge from the hospital with slight modifications, that is. paliperidone 6 milligrams (mg) twice a day (*BID)* (modified to paliperidone 6 mg once a day (*OD*), paliperidone palmitate 234 mg long-acting injection (LAI), and divalproex sodium 250 mg 3 times a day. In the month following her initial outpatient visit, the patient was hospitalized for another acute psychotic episode. Subsequently, paliperidone was replaced by risperidone 4 mg *OD*. Her positive symptoms improved, but she continued to be internally preoccupied with restricted affect. The combination of risperidone and divalproex sodium were complicated by a number of impairing side effects, (Table 1), leading to medication noncompliance by the patient and eventually prescription discontinuation by the psychiatrist. During the year following her initial outpatient appointment, a distinct episode of psychosis without mood symptoms, and several episodes of psychosis with prominent and persevering mood symptoms were noted. Throughout the course of her illness, psychotic symptoms were characterized by religious preoccupation, and persecutory delusions and mood symptoms were characterized by either expansive affect, pressured speech, and increased energy or low mood, anhedonia and lack of motivation, the latter being more frequent. In consideration of the combination of these presentations, the outpatient psychiatrist determined this a case of SAD, bipolar type. Imaging and urinalysis from hospital visits as well as the review of blood work were used to rule out organic causes. In the following years, psychotherapy, 11 sessions of ECT, and adequate trials of several different combinations of antipsychotics and mood

stabilizers were prescribed (Table 1). They all showed either partial effectiveness or were intolerable. Throughout these years, even when not in an acute episode, Patient J had residual delusions or mood symptoms. Moreover, she was unable to hold a job, drive, perform daily chores, and had difficulty taking care of her child. Depressive symptoms remained prominent for much of the time. This culminated in a suicide attempt in 2019. To determine that this is in fact a true case of treatment resistance and not pseudo-resistance, it was confirmed that the patient had undergone at least two adequate trials of antipsychotics (Table 1). Furthermore, there was evidence of therapeutic plasma levels of valproic acid (73 mcg/mL) during a 32-week trial of the drug, and paliperidone LAI was administered by injection at the doctor's office. Patient J was started on lumateperone 42 mg in January 2021. This resulted in a gradual but sustained response. It started with improvement in fatigue and an ability to "think more clearly." A month and a half later, the residual delusions were no longer elicited, and the patient denied hallucinations. There was also marked improvement in motivation. In summary, the patient has had no acute episodes while on lumateperone. She denies residual delusions and hallucinations. She has a steady job, drives, and socializes. Her affect is more pleasant, and she is not internally preoccupied. Her physical stressors of weight gain and fatigue have also gradually resolved. She continues to be stable, functional, and more independent than ever in the past 6 years at the time of the write-up of this report as per her latest appointment on 6/3/22.

All neuropsychiatric medications that had been prescribed before lumateperone and the reasons for their discontinuation are listed in Table 1.

Discussion

SAD has an estimated prevalence of 0.32%.[5] Evidence for treatment guidelines for SAD is limited, and mainly derived from Clinical Trials that concurrently enrolled patients with schizophrenia.[5] The treatment plan for SAD typically includes a combination of psychotherapy and pharmacotherapy with antipsychotics, mood stabilizers, and/or antidepressants, depending on the type.[12] Paliperidone is the only FDA-approved drug for SAD.[5,12] Interestingly, lumateperone has a similar structure and mechanism of action to paliperidone, which further points to a possible role for lumateperone in the treatment of this disorder.[13] In light of the scarcity of studies on the treatment of SAD, we believe case reports such as ours help identify potentially promising medications which warrant further investigation in future larger-scale observational and experimental research.

One of the reasons it took 6 years for a treatment to be adequately successful for Patient J was noncompliance, mainly due to excessive fatigue and weight gain. Patient-derived data indicates that extrapyramidal symptoms (EPS), sedation/cognitive, endocrine, and metabolic adverse effects are all significantly related to lower rates of adherence.[10,14] Moreover, according to studies investigating the safety of lumateperone in schizophrenia, in a range of lumateperone trials, from 4 weeks to >1 year, no adverse reaction had led to discontinuation at a rate above 2%.[14] Lumateperone did not lead to any intolerable side effects in our case study, either. It is argued that the lack of interaction between muscarinic and histaminergic receptors allows lumateperone to avoid the common adverse effects of antipsychotics[10] and the relatively low dopamine receptor D_2 (D_2R) occupancy explains the lower rates of EPS.[14]

The second roadblock precluding adequate recovery was the patient's cognitive deficits and negative symptoms. As was also observed in our case study, the limited efficacy of first-generation antipsychotics and SGAs in treating cognitive deficits and negative symptoms allows significant impairment of daily function.[10] The elucidation of the mechanisms through which lumateperone contributed to the treatment of these symptoms is essential not only to support its efficacy but also to shine light on promising pharmacodynamic properties for the treatment of cognitive deficit and negative symptoms.

Lumateperone exhibits some major differences in comparison to older SGAs. First, the ratio of 5-HT 2A receptor ($5HT\text{-}_{2A}R$): D_2R affinity is 60; significantly greater than in other SGAs.[14] Specifically, at steady state, the D_2R occupancy is less than 40%.[14] Furthermore, it exhibits a higher affinity for D2 receptors in the mesocortical and mesolimbic pathways than in the nigrostriatal pathway. This highly selective brain region targeting may also be a contributing factor to its favorable safety profile.[10] There is strong evidence for the antidepressant effects of lumateperone in preclinical assays as well as in clinical schizophrenia, and bipolar depression studies.[14] It is believed that its combined high occupancy of the serotonin 2A receptor $5\text{-}HT_{2A}R$ and its 5-HT-reuptake inhibition are the mechanisms behind its effectiveness in treating both depression symptoms as well as the negative symptoms of schizophrenia.[10,14] Its phosphorylation of *N*-methyl-d-aspartate receptor subunits and glycogen synthase kinase 3 beta has also been postulated to play a role in improving cognition and negative symptoms.[14]

Limitations

(1) While lumateperone has been effective for this specific case of SAD, it is important to acknowledge that patient-specific factors may have contributed to lumateperone's success. Hence, it cannot be assumed that lumateperone may be a silver bullet for all cases of SAD. Rather, in consideration of this case, we propose that patients with SAD with prominent symptoms of depression and intolerable side effects from other antipsychotics may benefit most from lumateperone's use.

(2) The case report is a retrospective description of 6 years of case notes from the outpatient psychiatrist following the patient. Most doctor notes from inpatient psychiatry, emergency room, and primary care for this patient were also available. However, not all the case notes were extensive and detailed. The imaging conducted to rule out organic causes was not available to the authors, who instead relied on the relevant notes by the radiologist and primary care physician.

Conclusion

The lack of presynaptic D_2 antagonism, the low D_2R occupancy, the high ratio of 5-HT_{2A} to D_2 receptor affinity, the enhancement of glutamatergic pathways, the evidence of efficacy in bipolar depression, and the absence of significant EPS and metabolic adverse effects all make lumateperone an exciting addition to the antipsychotic arsenal for SAD. However, as with all case reports, conclusions must be drawn with caution. Robust experimental studies investigating the role of lumateperone as a possible treatment option for SAD, including the evaluation of its efficacy in treating cognitive deficits and negative symptoms, as well as its role in both nontreatment-resistant and treatment-resistant patients, is required before a definitive verdict can be reached.

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Author contributions

M.H.S. Conceptualization, collection of case notes, analysis of case notes, literature search, writing; S.P. Editing, correspondence; S.K. Literature search, writing, editing; S.S.U.* Conceptualization, writing, analysis of case notes; S.L.* Conceptualization, writing, analysis of case notes; M.U. Editing, analysis of case notes; O.C. Williams: Supervision, planning; N.A. Supervision, conceptualization, and planning.

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