Long-Term Lumateperone Treatment in Bipolar Disorder: Six-Month Open-Label Extension Study

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Abstract

Introduction. Approved therapeutics for bipolar depression are associated with a range of undesirable side effects. Lumateperone (LUMA), a mechanistically novel antipsychotic that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, is FDA-approved for the treatment of schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder. The efficacy of LUMA in bipolar depression was previously established in two Phase 3 trials, as monotherapy (NCT03249376) and as adjunctive to lithium or valproate (NCT02600507).

A recent Phase 3 multi-center trial, Study 401 (NCT02600494) investigated the efficacy and safety of LUMA in bipolar depression and comprised a 6-week, randomized, double-blind, placebo-controlled period and a 6-month open-label extension (OLE) period. Here, we report the results of the OLE period, examining long-term safety.

Methods. Patients, aged 18–75 years, with a clinical diagnosis of bipolar I or II disorder who were experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and a Clinical Global Impression Scale-Bipolar Version, Severity [CGI-BP-S] score ≥4) were eligible for Study 401. Patients who completed the double-blind study were eligible for direct rollover into the OLE or were re-screened if completing the double-blind period prior to the initiation of the OLE. During the OLE, LUMA 42 mg was administered once-daily in the evening for 25 weeks.

The primary objective was safety and tolerability of LUMA as measured by incidences of adverse events (AEs) and changes in laboratory parameters, cardiometabolic measurements, electrocardiogram (ECG), and vital signs. The secondary objective was improvement/maintenance of symptoms of depression as measured MADRS and CGI-BP-S Total scores.

Results. A total of 127 patients were enrolled in the OLE, with 74 (58.3%) completing the study. Treatment-emergent AEs (TEAEs) occurred in 73 patients (57.5%) with 54 (42.5%) experiencing a drug-related TEAE. TEAEs that occurred in ≥5% of patients were headache, dry mouth, dizziness, nausea, somnolence, anxiety, and irritability. Most TEAEs were mild or moderate in severity. Extrapyramidal-symptom-related TEAEs were rare. Most patients who had normal metabolic laboratory values at baseline remained normal during the treatment period. Mean changes in blood pressure, pulse rate, ECG, and body morphology were minimal. Symptoms of depression improved as measured by the mean change from baseline to Day 175 in MADRS Total score (−8.9) and CGI-BP-S Total score (−2.3).

Conclusion. In patients with bipolar depression, long-term LUMA treatment was generally well tolerated with low risk of extrapyramidal symptoms, weight gain, and cardiometabolic effects. These data further support the safety, tolerability, and effectiveness of LUMA in patients with bipolar depression.

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Opioid-Induced Doctor Dolittle Phenomenon

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Abstract

Background. The Doctor Dolittle delusion, of animals conversing with the sufferer, has not heretofore been reported to occur with heroin intoxication.

Methods. This 23-year-old right-handed single male used heroin daily since the age of 19. For 2 years prior to presentation, 1 hour after injecting at least one bag of heroin IV, he developed hallucinations of animals talking to him. The voices would occur simultaneously with moving their mouths. Dogs would bark, cats would meow, and birds would squawk his name. Insects would engage him in friendly conversation. Different pitches of voice were produced from each animal; birds were high-pitched; squirrels, insects, and cats were lower-pitched; dogs were medium-pitched. As his intoxication resolved, the hallucinations also evaporated.

Results. Mental Status Examination: Oriented x 1, able to recall five digits forwards and three digits backwards. Able to remember none of four objects in 3 minutes without reinforcement and three with reinforcement. Able to spell the word "world" forwards but not backwards.

Discussion. The hallucination of animals talking, coincident with their mouths moving, articulating the words, associated with intoxication with high doses of heroin, with resolution with elimination of heroin, suggests opioid intoxication is the causative factor. The mechanism of zoopsia in Parkinson's disease has been attributed to dysfunction of the inferior longitudinal and inferior fronto-occipital fasciculi which relay visual information from the occipital cortex to the temporal and the orbitofrontal cortices. Heroin may have induced cortical inhibition, disinhibiting such pathways and thus facilitating these hallucinations. The simultaneous congruent auditory and visual hallucinations suggests a central origin of these, controlling both the auditory and visual system, such as the left superior and middle temporal gyrus, or possibly the cerebellar vermis. What is unique about the current description is that multiple animal and insect species were involved, and that the pitch of their voice was species specific (high-pitched in birds, and low-pitched in rodents and insects). The pitch may reflect the individual's personal hedonics towards the type of animal or the individual's interpretations of mass

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media's representation of these animals (i.e., cartoons of Looney Toons high-pitched Tweety Bird or Disney's low-pitched Jiminy Cricket). While it is possibly due to the opioids themselves, heroin is frequently adulterated with fillers which may contain hallucinogenic properties, any of which may have been the pathogenic factor. Autophobia, or the need for social contact, may be the nidus motivating such communicative anthropomorphism. Query as to the presence of such Doctor Dolittle hallucinations in those with heroin or other intoxicants may be revealing.
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Electroconvulsive Therapy in Thrombocytopenic Patients: A Case Report and Literature Review

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Abstract

Introduction. Electroconvulsive therapy (ECT) continues to be one of the most effective treatments for severe and treatment-resistant major depression. Although there are no absolute contraindications to performing ECT, the risks and benefits need to be assessed in all patients. We present a patient with a history of paroxysmal nocturnal hemoglobinuria (PNH) with significant thrombocytopenia, who completed an index course of six ECT sessions without complication. Currently, there are only two published case reports which describe the use of ECT in patients with thrombocytopenia.
Methods. AD is a 37-year-old female with a history significant for MDD, GAD, panic disorder, PNH, and Budd Chiari, who presented to ED for suicidal ideation. Initial labs showed pancytopenia (Hb 4.56 mg/dl, Absolute Neutrophil 0.7 x 10^3/mL). Given her history of multiple failed SSRIs, ECT was proposed to treat her depression. Anesthesia delayed her initial pre-operative assessment due to concerns regarding her platelet count and risk of bleeding. They recommended transfusion with a preprocedural platelet count goal of 50 x 10^3/mL. Psychiatry recommended a platelet goal of 20 x 10^3/mL given previous ECT literature. Patient underwent six ECT sessions without complications. Her platelets ranged from 24–40 x 10^3/mL and she did not require preprocedural platelet transfusion.
Results. Due to a lack of published literature, there are no formal guidelines for performing ECT in thrombocytopenic patients. The first case report details a 64-year-old female who underwent 12 ECT sessions without complication, while her platelet count ranged from 7–38 x 10^3/mL. The most recent case report describes a 74-year-old male who underwent nine ECT treatments without complications. The authors decided to transfuse prophylactically if pre-procedure platelet count was less than 20 x 10^3/mL. The patient underwent nine treatments, requiring eight transfusions. CT head did not show any signs of hemorrhage or structural changes. The authors remarked it is unclear whether the transfusions were necessary.
Conclusions. Even though ECT has been in use for over 80 years, there is still much that is unknown about this treatment modality. This case highlights the lack of absolute contraindications to performing ECT. However, the lack of literature and studies regarding platelet goals in thrombocytopenic patients for ECT delayed patient care in this specific case. We add a third case report in a thrombocytopenic patient who underwent ECT without complications with a pre-procedure transfusion criterion if platelet count was less than 20 x 10^3/mL. More research needs to be conducted to determine risk and cut-off limits for platelet transfusion prior to performing ECT in thrombocytopenic patients.
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Evaluating the Impact of Caffeine on the Incidence of Adverse Events During Treatment with Viloxazine Extended-Release (Qelbree®) in Adults with ADHD

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Abstract

Introduction. Viloxazine ER (viloxazine extended-release capsules (Qelbree®) is a novel, nonstimulant, FDA-approved treatment for attention-deficit/hyperactivity disorder (ADHD) in adults and children ≥6 years of age. Viloxazine ER inhibits cytochrome P450-1A2, the enzyme responsible for caffeine metabolism. In a Phase 1 study, the peak exposure (C_{max}) of caffeine was unchanged, while the systemic total exposure (AUC) was shown to increase ~5-fold following coadministration of caffeine (200mg) with viloxazine ER (900 mg/day x 4 days) compared to caffeine alone. Except for insomnia (44.4%), and possibly dizziness (8.3%), the incidence of adverse events (AEs) was not notably higher following coadministration vs. either caffeine or viloxazine ER alone. The objective of this analysis was to evaluate the impact of caffeine consumption on the incidence of AEs in adults with ADHD treated with viloxazine ER.
Methods. Data were analyzed from the Phase 3, double-blind (DB), placebo-controlled trial (NCT04016779) and ensuing (ongoing) open-label extension (OLE) safety trial (NCT04143217) supporting the viloxazine ER indication for adults with ADHD. Participants reported caffeine intake during the past week at each study visit.

Correlation was assessed between viloxazine ER dose (mg/day) and weekly total caffeine consumption (mg) and between ADHD Investigator Symptom Rating Scale (AISRS)

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