Abstract

Introduction. Lumateperone (LUMA) is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder. An open-label study (Study 303) evaluated the safety and tolerability of LUMA in outpatients with stable schizophrenia who switched from previous antipsychotic (AP) treatment. This post hoc analysis of Study 303 investigated the safety and tolerability of LUMA stratified by previous AP in patients who switched to LUMA treatment for 6 weeks.

Methods. Adult outpatients (≥18 years) with stable schizophrenia were switched from previous AP to LUMA 42 mg once daily for 6 weeks followed by switching to another approved AP for 2 weeks follow-up. Post hoc analyses were stratified by most common previous AP: risperidone or paliperidone (RIS/PAL); quetiapine (QET); aripiprazole or brexpiprazole (ARI/BRE); olanzapine (OLA). Safety analyses included adverse events (AE), vital signs, and laboratory tests. Efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions-Severity (CGI-S) scale.

Results. The safety population comprised 301 patients, of which 235 (78.1%) were previously treated with RIS/PAL (n=95), QET (n=60), ARI/BRE (n=43), or OLA (n=37). Rates of treatment-emergent AEs (TEAEs) while on LUMA were similar between previous AP groups (44.2%-55.8%). TEAEs with incidences of ≥5% in any AP group were dry mouth, somnolence, sedation, headache, diarrhea, cough, and insomnia. Most TEAEs were mild or moderate in severity for all groups. Rates of serious TEAEs were low and similar between groups (0%–7.0%).

Statistically significant ($P<.05$) decreases from baseline were observed in the OLA group that switched to LUMA in total cholesterol and low-density lipoprotein cholesterol with significant decreases thereafter on LUMA. Statistically significant decreases in prolactin levels were observed in both the RIS/PAL ($P<.0001$) and OLA ($P<.05$) groups. Patients switched from RIS/-PAL to LUMA showed significant ($P<.05$) decreases for body mass index, waist circumference, and weight. At follow-up, 2 weeks after patients switched back from LUMA to another AP, none of the decreases in laboratory parameters or body morphology observed while on LUMA maintained significance.

Those switching from QET had significant improvements from baseline at Day 42 in PANSS Total score (mean change from baseline −3.47; 95% confidence interval [CI] −5.27, −1.68; $P<.001$) and CGI-S Total score (mean change from baseline −0.24; 95% CI, −0.38, −0.10; $P<.01$).

Conclusion. In outpatients with stable schizophrenia, LUMA 42 mg treatment was well tolerated in patients switching from a variety of previous APs. Patients switching from RIS/PAL or OLA to LUMA had significant improvements in cardiometabolic and prolactin parameters. These data further support the favorable safety, tolerability, and efficacy of LUMA in patients with schizophrenia.

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Optimization of Sleep classification in Patients With Serious Mental Illness Using Accelerometer and ECG Data From a Wearable Patch

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Abstract

Introduction. Sleep is an important behavioral biomarker for patients with serious mental illness (SMI). The ability to accurately quantify sleep in a real-world setting could thus provide insight into patient well-being. In this study, patients in a sleep lab wore a patch that is part of a digital medicine system (aripiprazole with sensor (AS)) designed to provide objective records of medication ingestion. The patch provided accelerometer and electrocardiogram (ECG) data; polysomnography (PSG) data was collected to be used as the gold standard for sleep stage classification. The accelerometer and ECG data were used to build machine learning classification models to distinguish periods of wake from periods of sleep. To optimize these models for a real-world environment, different data sampling paradigms and methodologies were explored, and resultant model performances were analyzed.

Methods. Data was collected for a total of 220 nights, across 73 unique subjects—42 subjects had a diagnosed SMI (schizophrenia, bipolar disorder I, or major depressive disorder) and 31 subjects were healthy volunteers. PSG data, which provides a sleep stage designation at 30-second intervals, was combined into 5-minute windows, labeled as either "Sleep" or "Wake" based on which class comprised the majority of the 30-second intervals within the window. Accelerometer and ECG features were derived for each 5-minute window. Models were trained with three learning methodologies: a light gradient boosting machine (LGBM), a conditional random field (CRF), and a long short-term memory (LSTM) network. Model performance was tested with the full complement of accelerometer and ECG data, as well as down-sampled subsets of data. Additionally, ECG data from the PSG system was incorporated to test the effect of other ECG sampling strategies.

Results. CRF models produced the best classification performance (AUC = 0.91) with the full patch dataset. Down-sampling to include less than half of the accelerometer data did begin to degrade the specificity of the model. Down-sampling to include less frequent ECG collection did not have a significant effect on model performance; however, changing the sampling paradigm to continuous ECG collection from a block sampling paradigm did lead to more robust classification of when a patient was awake.

Conclusions. Accurately recording sleep in a logistically simple way can provide insights into the well-being of SMI patients. Combining these insights with the objective medication ingestion

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records provided by AS would be of great value to SMI patients, as well as their caregivers and physicians. This research explores what amount of sensor data is required to accurately quantify sleep and some of the machine learning strategies that can ameliorate data limitations, providing guidance for the optimization of digital device design.

Funding. Otsuka Pharmaceutical Development & Commercialization, Inc.

Viloxazine Increases Cortical Serotonin Without Inhibiting Serotonin Reuptake at Doses Used to Treat ADHD

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Abstract

Background. Most FDA-approved ADHD treatments increase norepinephrine (NE) and dopamine (DA); however, our prior preclinical studies of the non-stimulant ADHD treatment viloxazine ER (Qelbree®) demonstrated that viloxazine also increases serotonin (5-HT). A prior microdialysis study showed increases in NE, DA, and 5-HT in the rat prefrontal cortex (PFC); however, the 50 mg/kg dose resulted in supratherapeutic plasma concentrations. Viloxazine is a moderate affinity selective NE reuptake inhibitor, structurally different than traditional SSRI antidepressants. Viloxazine has negligible activity at the serotonin reuptake transporter (SERT), suggesting viloxazine has a different mechanism of 5-HT PFC elevation than SSRIs. The current microdialysis study was undertaken to further characterize if viloxazine affects 5-HT and its 5-HIAA metabolite at therapeutically relevant plasma concentrations. Results are compared to similar microdialysis studies of SSRIs.

Methods. Rats were implanted with I-shaped microdialysis probes connected to a microperfusion pump, delivering artificial cerebrospinal fluid, in the PFC. After a 2-hour baseline period, viloxazine (1, 3, 10, or 30 mg/kg) was administered (ip). Dialysate samples were collected from the interstitial fluid (ISF) of the PFC before and after dosing. LC-MS/MS was used to determine the dialysate concentrations of viloxazine and viloxazine-induced changes in NE, 5-HT, and their respective metabolites, DHPG and 5-HIAA. Viloxazine plasma concentrations were also measured.

Animal research was approved by the Institutional Animal Care and Use Committee and conducted in accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals.

Results. Viloxazine administration resulted in significant dose-dependent increases in ISF NE levels and corresponding decreases in DHPG (NE metabolite) at all doses tested, reflecting viloxazine's activity as a NET inhibitor. Viloxazine treatment also resulted in a dose-dependent elevation of ISF 5-HT levels in the PFC. Of the doses tested, 30 mg/kg was found to be clinically relevant as it induced ISF concentrations approximating unbound plasma concentrations in pediatric ADHD patients. At this dose, 5-HT levels were significantly increased over baseline and higher than vehicle levels. Coincident changes in 5-HIAA concentrations were not observed, reaffirming viloxazine's lack of activity as a SERT inhibitor.

Conclusion. Viloxazine induced dose-dependent increases in NE and 5-HT in the PFC, a critical target region for ADHD therapies. At clinically relevant viloxazine plasma concentrations, 5-HT was increased in the PFC. Unlike SSRIs, which correspondingly decrease the 5-HT metabolite in the PFC (indicating serotonin reuptake inhibition), viloxazine did not affect 5-HIAA levels. Thus, viloxazine increases cortical 5-HT levels by a different mechanism than SSRIs. Whether 5-HT effects aid in viloxazine therapeutic efficacy in ADHD is yet unknown.

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Safety And Tolerability of Aripiprazole 2-Month Ready-to-Use 960 mg in Adult Patients With Schizophrenia or Bipolar I Disorder

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Abstract

Introduction. Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a new long-acting injectable (LAI) antipsychotic formulation for gluteal administration every 2 months, intended for the treatment of schizophrenia and maintenance monotherapy treatment of bipolar I disorder (BP-I). This 32-week trial evaluated the safety, tolerability, and pharmacokinetic profile of multiple-dose gluteal administration of Ari 2MRTU 960 in clinically stable adult patients with a diagnosis of schizophrenia or BP-I, versus that of aripiprazole once-monthly 400 mg (AOM 400; an LAI indicated for the treatment of schizophrenia and maintenance monotherapy treatment of BP-I).

Methods. This was an open-label, multiple-dose, randomized, parallel-arm trial conducted at 16 sites in the US. Eligible patients (N=266) were randomized to receive Ari 2MRTU 960 every 56±2 days (n=132; 4 injections in total) or AOM 400 every 28±2 days (n=134; 8 injections in total). Safety and tolerability

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