Total score and caffeine consumption. Fifteen AE preferred terms, known to be associated with caffeine consumption, were evaluated. For viloxazine ER-treated subjects (200–600 mg/day) who experienced a potentially caffeine-associated AE, the probability the AE occurred as a function of viloxazine ER dose and caffeine consumption during the DB or OLE trials was estimated using a logistic regression model for AEs with an incidence ≥5%.
Results. Of 372 enrolled subjects ~85% reported caffeine use during the DB trial; mean caffeine use was 1034 mg/week for the placebo group and 859 mg/week for the viloxazine ER group. There was no correlation between viloxazine ER dose and caffeine consumption (p=0.73), nor between AISRS total score and caffeine consumption (p=0.908). Of subjects reporting caffeine use, 44 (DB placebo), 79 (DB viloxazine ER), and 33 (OLE viloxazine ER) reported any of the pre-identified caffeine- associated AEs and were included in the regression analysis. For these subjects, insomnia-related AEs, fatigue, nausea, headache-related AEs, decreased appetite, and somnolence-related AEs occurred in ≥5% of viloxazine ER-treated subjects. Based on the regression analysis, caffeine consumption significantly increased the probability of experiencing insomnia-related AEs only (p=0.02).
Conclusions. This analysis suggests using caffeine concomitantly with viloxazine ER does not increase the likelihood of experiencing caffeine-related AEs except for insomnia. Still patients should be aware of the potential for viloxazine ER to augment caffeine exposure.
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Characterization of Viloxazine Effects on Cortical Serotonin Neurotransmission at Doses Relevant for ADHD Treatment

Jennie Garcia-Olivares, PhD[1], Brittney Yegla, PhD[1], Jami Earnest, PharmD[1], Vladimir Maletic[2] and ChungPing Yu, PhD[1]

[1]Supernus Pharmaceuticals, Inc., Rockville, MD, USA and [2]Clinical Professor, Neuropsychiatry and Behavioral Science, University of South Carolina School of Medicine, Greenville, SC, USA and Consulting Associate, Division of Child and Adolescent Psychiatry, Duke University, Durham, NC, USA

Abstract

Introduction. Most ADHD treatments are thought to be effective due to augmentation of dopamine (DA) and norepinephrine (NE). Our prior preclinical studies found that the ADHD treatment, viloxazine, may augment serotonin (5-HT) in addition to NE and DA; however, it was unclear if these effects occurred at clinically relevant concentrations. To further understand these potential 5-HT effects, we conducted a series of experiments with two objectives: 1) Can we confirm and better elucidate the previously observed serotonergic effects of viloxazine and determine if they occur at clinically relevant concentrations? 2) Are these effects observed in species with close physiology to humans?

Methods. Objective 1: The affinity of viloxazine for human isoforms of 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 receptors was assessed via cell-based binding assays. Viloxazine agonism of 5-HT_{2C} and antagonism at 5-HT_7 was elucidated with IP_1, Ca^{2+}, β-arrestin, internalization, and cAMP assays in cells expressing human receptor isoforms. A microdialysis study was conducted in rats to determine the relationship between viloxazine concentrations in the interstitial fluid (ISF) and changes in NE, DA, 5-HT, and their metabolite concentrations in the prefrontal cortex (PFC). Objective 2: A PET imaging study using a 5-$HT_{2A/2C}$ radioligand agonist, [^{11}C]CIMBI-36, is being conducted in non-human primates (NHPs) to evaluate if viloxazine binds these receptors and/or increases 5-HT release.

Animal research was approved by animal care and use committees. Animals were cared for according to international standards.
Results. Objective 1: Cell-based assays to measure viloxazine affinity for NET, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 found K_i values of 0.14, 0.65, 0.84, 1.90 μM respectively. These values were lower than therapeutically relevant rat ISF concentrations (3.5 ± 1.6 μM) approximating pediatric ADHD patients unbound plasma concentrations (2.1-3.3 μM), indicating receptor recruitment. Binding affinity and functional activity assays found viloxazine had negligible activity for 5-HT_{2A} and SERT at therapeutic concentrations. Viloxazine 5-HT_{2C} agonism activated G_q-protein signaling (EC_{50}=1.6 μM, Ca^{2+} assay), but not β-arrestin or internalization pathways (EC_{50} values >150 μM). Viloxazine 5-HT_7 antagonism decreased G_s-protein signaling (IC_{50} =6.7 μM). The microdialysis study found that at therapeutically relevant ISF concentrations, 5-HT levels were significantly increased over baseline; no changes were seen in the 5-HIAA metabolite, indicating 5-HT increase is not due to 5-HT reuptake inhibition. Objective 2: PET imaging studies are ongoing.
Conclusions. To date, our experiments to further elucidate the potential 5-HT effects of viloxazine have shown that the previously observed effects of viloxazine on 5-HT receptors and its augmentation of 5-HT in rat PFC occur at clinically relevant concentrations. Further exploration is needed to ascertain if these effects occur in NHPs and are relevant to ADHD.
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Lumateperone 42 mg in an Open-Label Switch Study in Patients with Stable Schizophrenia: Results by Previous Antipsychotic

Andrew J Cutler, MD[1], John B Edwards, MD[2], Suresh Durgam, MD[2], Yifan Mo, PhD[2], Jazmin Acosta, PhD[2] and Robert E Davis, PhD[2]

[1]Department of Psychiatry, SUNY Upstate Medical University, Lakewood Ranch, FL, USA and [2]Intra-Cellular Therapies, Inc, New York, NY, USA

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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

Jeffrey M. Cochran, PhD

Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA

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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