Characterization of Viloxazine Effects on Cortical Serotonin Neurotransmission at Doses Relevant for ADHD Treatment

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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 serotoninergic 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-HT2A, 5-HT2B, 5-HT2C, and 5-HT7 receptors was assessed via cell-based binding assays. Viloxazine agonism of 5-HT2C and antagonism at 5-HT7 was elucidated with IP1, Ca2+-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-HT2A/2C radioligand agonist, [11C]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-HT2B, 5-HT2C, and 5-HT7 found Ki 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-HT2A and SERT at therapeutic concentrations. Viloxazine 5-HT2C agonism activated Gα-protein signaling (EC50 = 1.6 μM, Ca2+-β-arrestin assay), but not β-arrestin or internalization pathways (EC50 values > 150 μM). Viloxazine 5-HT7 antagonism decreased Gα-protein signaling (IC50 = 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

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Introduction. Most ADHAD 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 serotoninergic effects of viloxazine and determine if they occur at clinically relevant concentrations? 2) Are these effects observed in species with close physiology to humans?
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%).

Statistically significant (P < 0.05) 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 < 0.001) and OLA (P < 0.05) groups. Patients switched from RIS/PAL to LUMA showed significant (P < 0.05) 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 < 0.001) and CGI-S Total score (mean change from baseline –0.24; 95% CI, –0.38, –0.10; P < 0.01).

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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