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

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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 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

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