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.

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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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