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

Jennie Garcia-Olivares, PhD[1], Brittney Yegla, PhD[1], David Zweibaum, PhD[2], Jennifer Koch, PhD[1], Frank Bymaster, MS[3] and ChungPing Yu, PhD[1]

[1]Supernus Pharmaceuticals, Inc., Rockville, MD, USA, [2]Formerly with Supernus Pharmaceuticals, Inc., Rockville, MD, USA and [3]TRImaran Pharma, Inc., Nashua, NH, USA

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

Matthew Harlin[1], Murat Yildirim[2], Pedro Such[2], Jessica Madera-McDonough[1], Michael Jan[1] and Frank Larsen[2]

[1]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA and [2]H. Lundbeck A/S, Valby, Denmark

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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were evaluated throughout the study; assessments included adverse event reporting, patient reporting of injection site pain, and monitoring of extrapyramidal symptoms.
Results. In the Ari 2MRTU group, 102 patients (77.3%) completed the study; in the AOM 400 group, 92 patients (68.7%) completed the study. The overall incidence of treatment-emergent adverse events (TEAEs) was similar between Ari 2MRTU 960 and AOM 400 (71.2% versus 70.9%, respectively). The most frequently reported TEAEs were increased weight (22.7% for Ari 2MRTU 960 versus 20.9% for AOM 400) and injection site pain (18.2% for Ari 2MRTU 960 versus 9.0% for AOM 400), none of which were assessed as serious or severe by the investigators. All injection site pain events in the Ari 2MRTU 960 group were assessed as mild or moderate in severity; most (15.9%) coincided with the first injection and resolved within 5 days. Extrapyramidal symptom scores remained unchanged in both treatment groups.
Conclusions. Multiple-dose administration of Ari 2MRTU 960 was generally well tolerated in patients with schizophrenia or BP-I and did not show any new safety concerns.
Funding. Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Denmark)

Effect of Lumateperone (ITI-007) on Quality of Life and Functional Disability in the Treatment of Bipolar Depression

John B Edwards, MD[1], Suresh Durgam, MD[1], Susan G Kozauer, MD[1], Rakesh Jain, MD[2] and Roger S McIntyre, MD[3,4,5]

[1]Intra-Cellular Therapies, Inc., New York, New York, USA, [2]Department of Psychiatry, Texas Tech University School of Medicine – Permian Basin, Midland, Texas, [3]University of Toronto, Toronto, ON, Canada, [4]Department of Psychiatry, University of Toronto, Toronto, ON, Canada and [5]Department of Pharmacology, University of Toronto, Toronto, ON, Canada

Abstract

Introduction. In patients with bipolar disorder, depression symptoms are associated with greater reduction in function and quality of life than hypomania/mania symptoms. Lumateperone (LUMA), is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder.

In a recent phase 3 clinical trial (Study 404, NCT03249376) in people with bipolar depression, LUMA 42 mg monotherapy significantly improved symptoms of depression compared with placebo (PBO). This analysis of Study 404 investigated the effects of LUMA on functional disability and quality of life as measured using the secondary outcome measure, the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF).

Methods. Patients (18–75 years) with bipolar I or bipolar II disorder experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score ≥20 and Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score ≥4) were randomized to LUMA 42 mg or PBO orally, once daily in the evening for 6 weeks. The primary endpoint was the change from baseline to Day 43 in MADRS Total score, analyzed using a mixed-effects model for repeated measures (MMRM) approach in the intent-to-treat population (ITT). This post hoc analysis evaluated the mean change from baseline to Day 43 in the Q-LES-Q-SF individual item scores using an analysis of covariance with last observation carried forward (ANCOVA-LOCF) in the ITT. Categorical shifts in individual items were also analyzed.
Results. The ITT comprised 376 patients (LUMA 42 mg, 188; PBO, 188). Patients in the LUMA 42 mg group had significantly greater improvement on MADRS Total score change from baseline to Day 43 compared with PBO (least squares mean difference vs PBO [LSMD], −4.585; 95% CI, −6.344 to −2.826; effect size vs PBO [ES], −0.56; $P<.0001$). LUMA 42 mg treatment significantly improved Q-LES-Q-SF Total score from baseline to Day 43 compared with PBO (LSMD, 2.9; 95% CI, 1.15 to 4.59; $P=.001$).

The Q-LES-Q-SF items with the lowest mean scores at baseline in both groups were mood, leisure time activities, and sexual drive, interest, and/or performance. By Day 43, LUMA 42 mg treatment significantly improved 8 of the 14 items in the Q-LES-Q-SF ($P<0.05$). Overall life satisfaction also significantly improved with LUMA treatment ($P=.0016$). The largest improvements with LUMA 42 mg compared with PBO (ES>0.3,) were seen for the ability to function in daily life, family relationships, household activities, leisure time activities, and mood (all LSMD=0.3; all $P<.01$).
Conclusion. In patients with bipolar depression, treatment with LUMA 42 mg compared with PBO significantly improved patient quality of life and functional impairment. These results support LUMA 42 mg as treatment of MDEs associated with bipolar I or bipolar II disorder in adults.
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Rhabdomyolysis Caused by a Behavioral Manifestation of Acute Mania

Kalika Mahato[1], Alex Maben[1], Andi Ngo[2] and Ashish Sharma[2]

[1]University of Nebraska Medical Center, College of Medicine, Omaha, NE, USA and [2]University of Nebraska Medical Center, Department of Psychiatry, Omaha, NE, USA

Abstract

Introduction. While seen in patients with bipolar disorder due to NMS, antipsychotic side effects, or substance use, rhabdomyolysis resulting from behaviors seen in mania has not been reported in

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