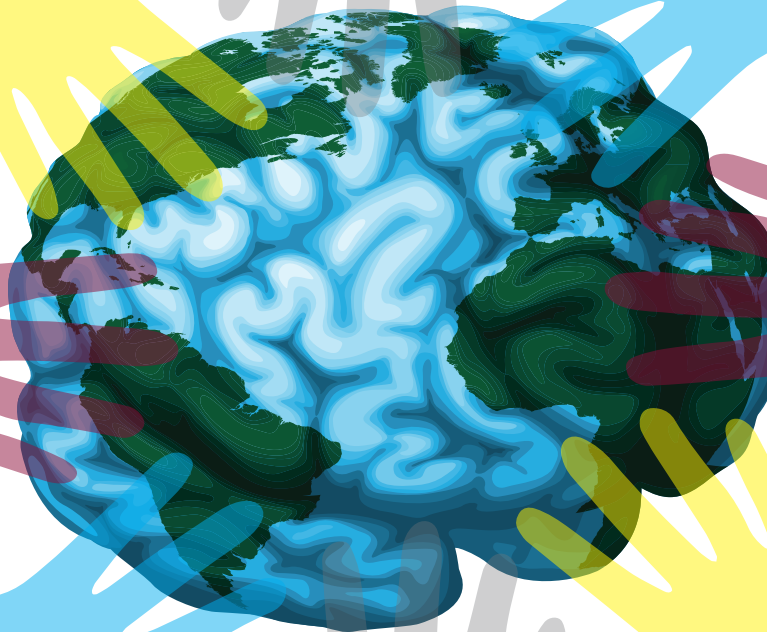


POSTER ABSTRACT BOOK

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Wednesday, May 31, 2017

Poster Session I

**W1. QUILLIVANT XR IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND ADHD: DOSE EFFECTS ON ADHD SYMPTOMS AND FUNCTIONING**

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**Abstract:** Introduction: ADHD symptoms are common in youth with Autism Spectrum Disorders. Stimulant medications are commonly used to treat ADHD symptoms in this population, although early studies suggest less efficacy and tolerability relative to youth with ADHD alone (Rupp, 2005). Quillivant XR® (QXR) is a long-acting liquid methylphenidate preparation that has been shown to significantly decrease ADHD symptoms in children with ADHD alone with an optimal dose range of 20mg to 60mg (Robb, Findling et al. 2014). We chose to evaluate the dose effects of a long-acting liquid methylphenidate on ADHD symptoms in youth with ASD and ADHD. We also sought to evaluate if an ASD symptom, social reciprocity, moderated response.

Methods: 36, 5-15-year old children (mean age 9.2) were recruited for the study evaluation, which included the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children--Present and Lifetime (K-SADS-PL) and the Autism Diagnostic Observation Schedule – 2nd edition (ADOS-2) for those that did not have a previous diagnosis of ASD. 27 participants met inclusion criteria for the 6-week trial and were randomized to one of the three treatment groups: Very Low Dose Group (starting dose of 5mg/day with potential max dose of 10mg/day), Low Dose Group (starting dose of 5mg/day with potential max dose of 20mg/day), or Moderate Dose Group (starting dose of 5mg/day with potential max dose of 40mg/day). At study completion, the maximum dose that all but one participant received in the Moderate Dose Group was 20mg/day. Therefore, the Low Dose and Moderate Dose groups were combined (renamed Medium Dose) and compared to the Very Low Dose group (renamed low dose). Primary outcome measures were the ADHD Rating Scale, version IV (ADHD RS-INV) and Clinical Global Impressions (CGI) completed by a rater blinded to treatment condition. Secondary outcome measures were the parent completed, Aberrant behavior checklist (ABC), Social Communication Questionnaire (SCQ), and HALP Sleep Questionnaire (HSQ). The Social Reciprocity Scale (SRS) was used as a moderator variable. Safety and tolerability was assessed weekly by monitoring vital signs and AEs and completion of the Response Impressions and Side Effects Checklist-Kids (RISC-K).

Results: The effect of time on ADHD total raw score overall was statistically significant (df=6,  $\chi^2=130.30$ ,  $p<0.0001$ ). There was no evidence for interaction between treatment group and time overall (df=6,  $\chi^2=10.75$ ,  $p=0.097$ ). When interaction terms between SRS total score and treatment group were included in the models for ADHD outcomes, there was no evidence for effect modification by SRS total ( $p=.497$  for ADHD Inattention Percent Score,  $p=.846$  for ADHD HI Percent Score, and  $p=.709$  for ADHD Total Percent Score). There were significant improvements from baseline on ABC Irritability, Lethargy, Hyperactivity, and Inappropriate

Speech for the medium dose titration group ( $P < 0.1$ ), while the low dose group did not display improvement. There were no serious adverse events.

Discussion: QXR shows considerable promise in treating ADHD symptoms in the context of ASD. Both low and medium dosing schedules were associated with significant reductions in ADHD symptoms in children with ASD and ADHD, while the medium dose group was also associated with beneficial effects on secondary outcome measures from the aberrant rating scale. Using a slow, flexible dose titration resulted in excellent tolerability and compliance in a difficult to treat patient group.

## **W2. LONG-TERM EFFICACY AND SAFETY OF EXTENDED-RELEASE MOLINDONE (SPN-810) TO MANAGE IMPULSIVE AGGRESSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

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**Abstract:** Background: This study sought to assess overall clinical response during long-term use (up to 6 months) of extended-release molindone (SPN-810), a dopamine D2/D5 receptor antagonist, to manage impulsive aggression (IA) in children 6-12 years old with attention deficit hyperactivity disorder (ADHD) concurrently treated with an FDA-approved dose of a stimulant or atomoxetine.

Methods: Patients who completed the Phase 2B, double-blind (DB), placebo-controlled, dose-ranging study were enrolled in an open-label extension (OLE) in which SPN-810 dosages were adjusted according to clinical response after blinded conversion to 18 mg ( $<30$  kg) or 36 mg ( $\geq 30$  kg). For the DB study, patients had to have ADHD diagnosis and a Retrospective-Modified Overt Aggression Scale (R-MOAS) score  $\geq 24$  at screening and  $\geq 20$  after a 3-week OL stimulant optimization period. Key endpoints presented include adverse event (AE) occurrence and change in R-MOAS score.

Results: Of 78 patients entering the OLE, 52 (67%) completed it. Most common reasons for discontinuation were consent withdrawn (11.5%), AEs (9%), lost to follow-up (6%), and investigator decision (4%). Most common AEs considered possibly/definitely related to study medication were sedation (11.5%), increased appetite (9%), weight gain (8%), and somnolence (5%). Treatment-related AEs were dose related (9 mg/day, 13%; 36 mg/day, 33%). Two patients developed symptoms suggestive of extrapyramidal symptoms (dyskinesia,  $n=1$ ; dystonia,  $n=1$ ), which resolved with dose reduction ( $n=1$ ) or with no action taken ( $n=1$ ). Treatment-related AEs resulting in discontinuation ( $n=5$ ) included aggression ( $n=2$ ), weight gain ( $n=2$ ), and tachycardia ( $n=1$ ). There were no notable or systematic effects on laboratory assessments, vital signs, or ECGs. Median R-MOAS changes from DB baseline were -31.5, -25.0, and -27.0 at OLE maintenance doses of 18, 27, and 36 mg/day, respectively; median R-MOAS changes from OLE baseline were 0, 10, and 0 at OLE maintenance doses of 18, 27, and 36 mg/day, respectively.

Conclusions: Improvements in patients with IA behavior achieved with SPN-810 treatment (R-MOAS change from DB baseline) were sustained during OLE treatment (stable R-MOAS score from OLE baseline). SPN-810 was generally well tolerated, and there was a relatively low rate of discontinuation due to AEs. AEs were consistent with the types of events expected in children receiving low-dose SPN-810 added to ADHD medication.

### **W3. ANXIETY AS A CONFOUNDING SYMPTOM IN ADHD TRIALS**

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**Abstract:** Introduction: In both childhood and adult studies of ADHD a relatively large portion of subjects have high levels of anxiety symptoms.<sup>1</sup> These symptoms might reflect independent co-morbid anxiety disorders, or overlap between ADHD and anxiety. We collected data from several ADHD trials and clinic samples that included measures of both areas. These cohorts contained significant numbers of subjects with high levels of anxiety symptoms.

Methods: Either the Symptom Check List – 90 (item average scores of at least “moderate”) (SCL-90) or the Hamilton Anxiety Scale (scores of 14 or higher) (HAM-A) were used to identify groups with high levels of anxiety. Baseline differences between the high versus low anxiety groups were examined relative to demographics and initial ADHD symptoms. The impact of anxiety on attrition and improvement in ADHD symptoms was assessed. ADHD symptoms were determined using the CARRS or the AISRS in addition to the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS). The WRAADDS contains 2 factors, Attention and Emotional Dysregulation, and allows subjects to be classified as ADHD Attention or Emotional Dysregulation Presentation.<sup>2</sup>

Results: In several of the studies, the incidence of increased anxiety was greater in women with ADHD. Initial level of anxiety did not predict response of ADHD symptoms to treatment, and this finding was not changed when gender was taken into account. In 3 of the 4 cohorts there was a significant, but low correlation between initial anxiety and the Attention factor of the WRAADDS (range  $r=.160$  to  $r=.245$ ). In all of the cohorts there was a significant association of initial anxiety with the Emotional Dysregulation factor (range  $r=.206$  to  $r=.329$ ). Subjects with high anxiety had significantly higher Hamilton Depression scales than those with low anxiety ( $p<.007$ ). Patients with elevated anxiety showed good drug-placebo differences in ADHD assessments. Within all trials, anxiety symptoms decreased during treatment. But there was no drug-placebo difference in improvement. Anxiety was not associated with subject attrition during the clinical trials.

Conclusions: A significant number of subjects in ADHD clinical trials have elevated levels of anxiety, but these symptoms did not alter treatment response or increase attrition. Anxiety in ADHD subjects is related to a limited extent to both symptom factors measured by the WRAADDS.

### **W4. GLUTAMATERGIC NETWORK GENE MUTATIONS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)**

*Josephine Elia<sup>2</sup>, Celia Kim<sup>3</sup>, Munir Khan<sup>3</sup>, Diego R. Mazzotti<sup>3</sup>, Hakon Hakonarson<sup>3</sup>, Colleen Anderson<sup>1</sup>, David Fitts<sup>1</sup>, Liza Squires<sup>\*1</sup>*

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**Abstract:** Objective: To estimate prevalence of rare, recurring copy number variants (CNVs) of specific metabotropic glutamate receptor (GRM) and related network genes in a pediatric population with ADHD and to explore associated phenotypes.

Methods: Multiple lines of evidence support glutamatergic involvement in ADHD pathogenesis, including significant association between ADHD occurrence and loss-of-function mutations (CNVs) in GRM gene family and interacting genes (Elia J et al. Nature Gen 2012; 44:78-84). A multicenter (n=23), noninterventional study enrolled children/adolescents with ADHD, collecting saliva samples for analysis (273 genes) by Children's Hospital of Philadelphia genotyping laboratory. Phenotypic assessment was based on questionnaire-directed interview to elicit ADHD symptoms and medical history, ADHD treatment history, psychiatric comorbidity, development/education history, and current behaviors of concern.

Results: Of 1013 children/adolescents with ADHD (6 - <12 yrs, n=291; 7-12 yrs, n=722), 220 subjects were mutation-positive (Prevalence: overall, 22%; children, 26%; adolescents, 20%). The demographic profile of mutation-positive subjects was consistent with expectations for a clinical pediatric/adolescent ADHD population – predominantly male and ADHD Combined as most common presentation. Mutation-positive subjects were significantly more likely to have parent-reported disruptive behaviors, anger control issues, and inappropriate movements.

Conclusion: In this clinical US population of children/adolescents with ADHD, the 22% observed prevalence of glutamatergic network mutations suggests that a substantial proportion of ADHD population may be candidates for glutamate-modulating therapy. GRM mutation positive subjects displayed a higher prevalence of behaviors associated with emotional dysregulation. The study population has been increased to nearly 2000 subjects to better characterize the potential relationship between mutation status and phenotypic traits and comorbidities. Results of an interventional trial of the glutamate modulator AEVI-001 in adolescents with GRM mutation-positive ADHD will enhance understanding of targeting glutamatergic pathways in ADHD. Study sponsored by Aevi Genomic Medicine.

#### **W5. DO OPIATE ANTAGONISTS INTERFERE WITH THE CLINICAL BENEFITS OF STIMULANTS IN ADHD? A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE MIXED OPIOID RECEPTOR ANTAGONIST NALTREXONE**

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**Abstract:** Objective: Methylphenidate (MPH) activates mu opioid receptors, which are linked to euphoria. Mu opioid antagonists, such as naltrexone, may attenuate the euphoric effects of stimulants, thereby minimizing their abuse potential. This study assessed whether the combination of naltrexone with MPH is well-tolerated while preserving the clinical benefits of stimulants in subjects with ADHD.

Method: We conducted a six-week, double-blind, placebo-controlled, randomized clinical trial of naltrexone in adults with DSM-IV ADHD receiving open treatment with a long acting formulation of MPH. (January 2013 to June 2015) Spheroidal Oral Drug Absorption System (SODAS)–MPH was administered BID and titrated to ~1 mg/kg/day over three weeks and continued for three additional weeks depending on response and adverse effects. Subjects were adults with ADHD preselected for having experienced euphoria with a test dose of immediate

release (IR) MPH. The primary outcome measure was The Adult ADHD Investigator Symptom Report Scale (AISRS).

Results: Thirty-seven subjects who experienced stimulant-induced (mild) euphoria on a baseline visit were started in the open trial of SODAS MPH and randomized to 50 mg naltrexone or placebo. Thirty-one subjects completed through Week 3, 25 through Week 6. Throughout six weeks of blinded naltrexone and open MPH treatment, the co-administration of naltrexone with MPH did not interfere with the clinical effectiveness of MPH for ADHD symptoms. Additionally, the combination of naltrexone and MPH did not produce an increase in adverse events over MPH alone.

Conclusion: Our findings provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential.

## **W6. EFFECT OF SEDATIVE HYPNOTIC MEDICATIONS ON SLEEP IN OPIOID-DEPENDENT SUBJECTS ON BUPRENORPHINE**

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**Abstract:** Purpose: Buprenorphine is regularly used in the treatment of opioid use disorders with a recent federal mandate to increase its availability for this purpose. Sleep disturbances are common in both opioid abstinence and buprenorphine treatment (1,2). Patients with opioid use disorders on bu-prenorphine (OUDs) may self-medicate with over-the-counter hypnotics (containing diphenhy-dramine, melatonin, doxylamine) or be prescribed sedating antidepressants (such as trazodone or mirtazapine) or sedating antipsychotics (such as quetiapine). They may also find ways to ac-quire GABAergic hypnotics, which are not usually prescribed in addiction treatment because of abuse risk. The literature is uninformative on the frequency of prescribed or self-medicated treatment of sleep disturbances in buprenorphine-treated patients. We sought to calculate this frequency and evaluate the efficacy of sleep aids in OUDs using self-reported measures of sleep quality.

Methodology: OUDs (n=138) were recruited from a buprenorphine maintenance program in central Pennsylvania. Subjects completed a sociodemographic survey and the Pittsburgh Sleep Quality Index (PSQI), then were divided into two groups: OUDs taking sleep aids (OUDSA) and those who were not (OUDN). We used a modified PSQI total score by subtracting out PSQIMEDS. This allowed us to compare overall sleep quality without artificially inflating the PSQI scores of the patients in the sleep aid group, who had higher PSQIMEDS scores than the patients not taking sleep aids. A modified PSQI score of >5 indicates poor sleep quality. Student t-tests were used to compare sleep latency, total sleep time, sleep efficiency, and modified PSQI total score. A Mann-Whitney U test was used to compare anxiety (on the sociodemographic questionnaire) between the groups.

Results: There were 40/138 (29%) subjects taking sleep aids. Over-the-counter medications were reported by 15/40 (38%) and included melatonin (n=5), diphenhydramine (n=7), doxylamine (n=3). Prescription medication usage was reported by 19/40 (48%) patients and included quetiapine 100 to 600 mg (n=4), trazodone 50 to 200 mg (n=3), mirtazapine 15 to 30 mg (n=3), gabapentin 300 to 600 mg (n=3), temazepam 15 mg (n=1), clonazepam (n=1), and amitriptyline 10 mg (n=1). There were 6/40 (14%) patients on unknown medication. There was no difference

between the groups on the modified PSQI total score (OUDSA=9±4, OUDN=8±4,  $p>0.05$ ); however, both groups still had a modified PSQI score of >5. Both groups also had prolonged sleep latency (OUDSA=44±49, OUDN=41±40,  $p>0.05$ ), lower total sleep time (OUDSA=6±2, OUDN=6±2,  $p>0.05$ ), and lower sleep efficiency (OUDSA=80±21, OUDN=81±21,  $p>0.05$ ) than are considered normal. There were statistically significant higher anxiety scores in OUDSA compared to OUDN ( $U=1315.5$ ,  $p=0.002$ ).

Conclusion: One third of OUDs are on various sleep aids including prescription and nonprescription meds which are not FDA approved for sleep disturbance. Sleep medications do not appear to successfully address sleep disturbance in this population as there was no difference between the groups on sleep latency, total sleep time, sleep efficiency or PSQI total score, (with PSQIMEDS removed). There is a further need to explore better pharmacological and behavioral treatments to address sleep disturbance in OUDs and thereby prevent relapse.

## **W7. SAFETY, PHARMACOKINETIC, AND PHARMACODYNAMIC EVALUATION OF A NORIBOGAINE MULTIPLE-DOSE REGIMEN IN OPIOID-DEPENDENT SUBJECTS**

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**Abstract:** Specific Purpose and Content: Noribogaine (NI) is an active metabolite of ibogaine and may be more selective in treating opioid dependence without undesirable psychotomimetic effects. Previous clinical studies evaluated single doses of NI and suggested that it is safe and well-tolerated, but with a concentration-dependent increase in the QTc interval. This study evaluated the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of NI after multiple dosing of NI HCl capsules in treatment-seeking opioid-dependent subjects.

Methods: This was a phase 1B, open-label, titration study conducted in an inpatient clinical unit. A loading dose of oral NI 80 mg was followed by titrated maintenance dosing (10, 20, 30, or 40 mg, q6h) for up to 5 days. Maintenance dosing algorithm considered subjective and objective clinical assessments and QTcF to avoid pronounced QT prolongation (QTcF >500 msec or  $\Delta$ QTcF >60 msec was exclusionary). Standard safety evaluations, PK, and PD assessments (eg, opioid withdrawal and mood scales) were conducted. Continuous cardiac monitoring was performed via Holter monitor and telemetry.

Results: Nine subjects (6 males; mean age 31.2 years) were enrolled. Opioid use included heroin and prescription opioids. Cumulative NI doses ranged from 80 mg to 670 mg, with 4 subjects administered the maximum 20 doses (mean 653 mg, range 640–670 mg). No serious adverse events (AEs) were reported. Of 140 treatment-emergent AEs, 96% were mild in severity, none were severe and 58% were opioid withdrawal-related. NI plasma concentrations showed high inter-subject variability, even between subjects with similar unit/daily/total doses. C<sub>max</sub> values following multiple dosing ranging from 52 to 252 (mean 102) ng/mL. The largest  $\Delta$ QTcF by subject ranged from 22–51 msec (mean 33 msec). A concentration-dependent increase in  $\Delta$ QTcF was observed, corresponding to a predicted  $\Delta$ QTcF of 17 msec at the geometric mean peak concentration of 89.1 ng/mL. No QTc changes resulted in AEs or

discontinuation. Scores on withdrawal and mood scales improved rapidly and substantially following administration of NI, and this was supported by non-solicited self-reports that the withdrawal experience was less severe compared with previous attempts in the majority of subjects. Mean (SD) Subjective Opiate Withdrawal Scale (SOWS) score at baseline was 30.3 (10.6) and declined to 16.8 (7.4) one hour after loading dose administration; at 51 hours post-loading dose, mean SOWS score was 10.4 (9.7). Mean (SD) Profile of Mood States (POMS) total mood disturbance (TMD) score was 53.8 (22.2) at baseline and declined to 37.3 (43.3) at 57 hours post-loading dose. All 4 subjects who remained in the clinic after 72 hours experienced further decreases in withdrawal and mood scores (SOWS: 4.8 (4.9) at 81h; POMS TMD: 0.8 (4.6) at 84h). Subjects returned to their pre-treatment environment, largely devoid of support; 5 subjects relapsed, 3 were lost to follow-up, and 1 remained abstinent (15 weeks). Conclusions: NI treatment for up to 5 days was well tolerated. The previously noted QTc effect was confirmed, and a dosing algorithm with QTc criteria was successful in avoiding pronounced QTc prolongation (ie, no QTcF >500 msec or  $\Delta$ QTcF >60 msec). Steady-state NI concentrations were reached rapidly with the use of a loading dose. Clinically significant reductions in withdrawal symptoms and mood assessments were seen following NI administration. These findings support continued evaluation of NI in treating opioid dependence under medical supervision in controlled clinical trials.

#### **W8. ADOLESCENT SOCIAL STRESS RESULTS IN SEX-SPECIFIC TRANSCRIPTIONAL REPROGRAMMING OF THE MEDIAL AMYGDALA, A CRITICAL REGION FOR SEX DIFFERENCES IN REWARD**

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**Abstract:** Adolescence is a time of heightened sensitivity to rewarding stimuli and is associated with increased vulnerability to psychiatric disorders. Stress during this period results in long-term changes in adult behavior. Adolescent social isolation (SI) has been used as a rodent model for addiction susceptibility in humans and has been shown to alter neuronal morphology, physiology and gene expression throughout the reward circuitry and increases preference for drugs of abuse in male rodents. However, little is known about how females respond to such stressors. The medial amygdala (meAMY) is a sexually dimorphic region that develops during adolescence and is sensitive to perturbations at this time. Our preliminary data suggest that SI not only reverses sexually dimorphic reward-related behaviors but permanently reduces baseline sex differences (M>F) in neuronal projections from the meAMY to ventral tegmental area (VTA). Therefore, we tested the hypothesis that SI results in persistent transcriptional changes in the meAMY that underlie such sex differences. Mice were socially isolated or group housed (GH) from postnatal day (P) 22 - P42, then GH until adulthood (~P90). Micropunches from the meAMY as well as the VTA and prefrontal cortex (PFC), two regions receiving input from the meAMY, were collected and transcriptome-wide changes investigated by RNA-sequencing after acute or chronic cocaine or saline (7.5mg/kg) (n = 5 – 8/group). Those genes displaying a sex X stress interaction were significantly enriched in sexually dimorphic genes in all 3 brain regions (p < 0.001) with the greatest number of transcripts affected in the meAMY (869). However, expression was not altered by SI alone, suggesting that sexually dimorphic genes are preferentially altered by adolescent stress. Additionally,



hierarchical clustering revealed that SI reversed baseline sex differences in gene expression in all 3 regions, similar to the differences observed in behavior. Specifically, GH males cluster with SI females and vice versa for those genes displaying a sex X stress interaction in the meAMY, VTA (276 genes) and PFC (495 genes). To determine if sex differences in the response to cocaine were also reversed by SI, hierarchical clustering was used to analyze how those genes displaying a sex X stress interaction responded to drug. In the meAMY and VTA, sex differences in response to chronic but not acute cocaine are reversed by SI suggesting that the meAMY to VTA projections are important for the regulation of sex differences in reward. These data suggest that adolescence is a sensitive period for development of sex differences in brain connectivity as indicated by reduction of sex differences in meAMY to VTA neuronal projections. Additionally, adolescent stress causes sustained reversal of sexually dimorphic gene expression in key limbic brain regions. Current work is focused on identifying novel therapeutic targets in the meAMY that can influence addiction-related behaviors in individuals with increased sensitivity to cocaine (SI males and GH females) by comparing transcriptome-wide changes in those animals displaying less sensitivity to cocaine (GH males and SI females).

## **W9. IDENTIFYING SUB-POPULATIONS OF HEAVY DRINKERS: A SWEET ROAD TO A BETTER PHENOTYPIC CHARACTERIZATION?**

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**Abstract:** The search for new approaches to refine the diagnosis of alcohol use disorder accurately are underway. An association between alcohol use disorder and preference for high sweet solutions has been previously described, and linked not only to individual's family history of alcoholism but also to some personality traits such as novelty seeking. Using a sweet preference test that is reliable and easy to administer, most likely in a combination with personality or other alcohol-related traits, could not only present a way to develop novel approaches to improve the clinical approach to alcohol use disorder, but could also open the door to the possibility of providing better tailored treatment.

In order to better understand how and why sweet preference phenotype can be leveraged in the context of alcohol use disorder, we conducted a study aiming mainly at describing and comparing subpopulations of heavy drinkers based on their sweet liker status, through their trait, behavioral and metabolic differences and similarities.

A group of heavy drinkers completed a sweet taste test along with a series of trait and behavioral assessments. Participants were asked to sip and spit each of 5 solutions (0.05, 0.10, 0.21, 0.42 and 0.83 M), and rate how sweet was the taste (i.e., intensity) and how much they liked the taste (i.e., pleasantness). Participants with higher pleasantness rating for the 0.83M solution were classified as sweet likers (SL), all the others were classified as sweet dislikers (SDL).

Out of 55 patients who completed the sweet preference test, 20 (36%) were SL and 35 (64%) were SDL. As a first step, we compared the two groups with regards to their characteristics, as well as range of traits and behaviors that are shown to play a role in alcohol intake. There were no group differences in age ( $p=.88$ ) or body mass index ( $p=.45$ ) between SL and SDL. However, there was a higher representation of males in the SDL group (70%) compared to the

SL group (30%;  $p=.007$ ), but no differences among females ( $p=.36$ ). Of the 24 individuals with no family history of alcohol problems, a higher prevalence was observed in the SDL (75%) versus the SL (25%;  $p=.01$ ). Of the 23 non-smokers in the sample, a higher prevalence was observed in the SDL (78%) vs the SL (22%;  $p=.007$ ). Results also indicated distinct associations of traits between likers and dislikers, as for instance a higher trait anxiety was associated with a higher food craving among the SL ( $r=.55$ ;  $p=.01$ ) but not the SDL ( $r=-.002$ ;  $p=.99$ ). The SL status also seems to play a role in the association between food craving and perception of the subjective effects of alcohol: the higher the SL emotional craving for food ( $r=-.52$ ;  $p=.02$ ) and their preoccupation with food ( $r=-.51$ ;  $p=.02$ ) were, the lower number of drink they needed to feel the effects of recent alcohol intake; by contrast, these associations were not observed in SDL. A subset of the participants ( $n=21$ ) completed the obsessive compulsive drinking scale. Total craving ( $p<.0001$ ), obsessive ( $p<.0001$ ) and compulsive drinking ( $p=.002$ ) were higher in the SL ( $n=7$ ) compared to the SDL ( $n=14$ ). Although the sample is small, these results further strengthen the need to look at these subpopulations separately and how their specific profile could help tailor treatment.

These preliminary results indicate differences within heavy drinkers based on SL status, prompting broader questions about the relationship between status and specific alcohol-related aspects. Analyses are needed to describe possible clusters that could be leveraged for clinical and research endeavors as well as moving the field forward towards a tailored more precise treatment and treatment plan for heavy drinkers and alcohol dependent individuals based on their specific profile and needs.

#### **W10. A PROOF OF CONCEPT TRIAL OF A NOVEL COMBINATION OF METHYLPHENIDATE AND ONDANSETRON FOR TREATMENT OF STIMULANT USE DISORDER**

*Steven Szabo, Ashwin Patkar\*, Shein Chow, Tong Lee*

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**Abstract:** Objective: There are currently no approved pharmacologic agents which have shown convincing efficacy in the treatment of cocaine or methamphetamine use disorder (collectively termed “stimulant use disorder” or SUD). We previously described our translation effort toward a regulatory approval of a novel combination drug treatment, derived in part from our preclinical results using behavioral sensitization and self-administration models of SUD in rodents (Lee et al., 2012, Drug Alcohol Dep. 124:11-18). In a proof-of-concept Phase IIA trial in abstinent SUD patients (single-site, randomized, double-blind design), we determined efficacy of a combination of an immediate-release methylphenidate formulation (MPh-IR) and a novel ondansetron formulation (Ond-PR2), using standard cue-reactivity and resting-state neuroimaging paradigms.

Methods: Subjects were treated with either 20 mg MPh-IR + 8 mg Ond-PR2 ([MPh-IR + Ond-PR2]) or identical-appearing placebo (dextrose) for 2 weeks under a protocol approved by the Duke University Health System Institutional Review Board. The neuroimaging procedures were performed 1-7 days before and 2-7 days after the 2-week treatment.

Results: A total of 48 patients were screened and 30 qualifying subjects were randomized into either [MPh-IR + Ond-PR2] or placebo treatment group. Twenty-eight subjects completed the 2-week drug treatment and pre- and post-treatment fMRI assessments. Compared to placebo, [MPh-IR + Ond-PR2] induced significant changes in the cue-induced activation in selected prefrontal, parietal and anterior cingulate cortical areas. Furthermore, “seed-to-voxel” analyses

showed reduced resting-state connectivity between selected cortical and striatal/cerebellar areas following [MPh-IR + Ond-PR2] treatment. The active treatment group also reported significantly reduced “craving” scores (drug – neutral cues) during the post-treatment fMRI session. There were no clinically significant adverse events observed with drug treatment. Conclusions: These results suggest that [MPh-IR + Ond-PR2] might provide for an effective option for SUD treatment. Further randomized controlled trials with large sample sizes are necessary to confirm the findings.

## **W11. OPTIMIZING CLINICAL OUTCOMES: A COMPARISON OF ESTIMATED BAC AND SELF-REPORT STANDARDS FOR HEAVY DRINKING**

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**Abstract:** Identifying outcomes that are likely to translate to meaningful improvements in health is critical for clinical research. In the field of alcoholism, a commonly used outcome is no heavy drinking days. Heavy drinking is typically defined as days when a man consumes at least 5 standard drinks or a woman consumes at least 4 standard drinks. An important question is how sensitive and specific this current 5/4 heavy drinking definition is for a blood alcohol content (BAC) level above 0.08%, representing the legal limit for driving that has been associated with reproducible behavioral impairment. Furthermore, altering the required time period over which heavy drinking occurs or the quantity of drinks consumed may optimize this measure. Using baseline data from a clinical trial of 131 individuals with alcohol use disorder who also smoked cigarettes, we performed a secondary analysis comparing different heavy drinking measures against a calculated estimate of BAC, which incorporates total body water and length of time over which drinks are consumed. Using estimated BAC  $\geq 0.08\%$  vs.  $< 0.08\%$  as the gold standard, we found that the 5/4 heavy drinking definition misclassified 25/129 individuals, with a sensitivity of 96% and specificity of 60%. Part of this low specificity is likely attributable to variations in the time period over which drinking occurred. Individuals who consumed drinks over longer time periods may not achieve a high estimated BAC. In this trial, the duration of drinking was significantly longer for those that met the 5/4 heavy drinking criteria (average 336 minutes) compared to those that did not (average 158 minutes) ( $p < 0.0001$ ). A more recent definition of binge drinking is the consumption of 5/4 standard drinks within a 2-hour period based on the reasoning that a typical adult is expected to achieve a BAC of greater than 0.08 during this time. In comparison to estimated BAC as the gold standard, the 5/4 definition within 2 hours for binge drinking had a specificity of 100% but a sensitivity of 51%. This illustrates how restricting the time period over which heavy drinking occurs can improve specificity at the cost of sensitivity. Longer time specifiers yielded better sensitivity without a large reduction in specificity. Similarly, increasing the threshold for number of drinks above the 5/4 definition (e.g. 6/5 or 7/6) improves specificity at the cost of sensitivity. These empirically based results suggest that using the standard 5/4 heavy drinking definition may misclassify a large proportion of individuals based on estimated BAC. Restricting the duration of drinking or increasing the threshold of drinks may improve the accurate identification of individuals who experience heavy drinking. These results are directly relevant for the selection and further development of clinically meaningful brief outcome measures. As drinking behaviors and population demographics across the United States

change, it is important to continue to assess whether outcome measures reflect biologic changes.

## **W12. THE ROLE OF THE BLACK CHURCH IN IMPROVING TREATMENT ACCESS FOR BLACKS WITH SUBSTANCE USE DISORDERS**

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**Abstract:** Substance use disorders are one of the most devastating health and social issues confronting this country, and disproportionately affect minority communities. Black adults use alcohol at lower rates compared with their white counterparts, with nicotine and illicit drug use at the same rate; however, Blacks are more likely to suffer negative drug-related consequences. Despite this disparity, Blacks are less likely to initiate substance use treatment when compared with other racial groups. Societal and cultural stigma, mistrust of the medical system, lack of health care coverage, circuitous pathways to care, lower socioeconomic status, and the absence of culturally informed treatment have all been cited for low treatment initiation and engagement among Blacks. The Black Church, a highly trusted entity in Black communities, may serve as a promising setting for the recruitment and treatment of Black Americans with substance use disorders (BSD), given prior successes in addressing stigmatized conditions, such as HIV and depression, along with decreased substance use, when traditional care was coupled with church support. Delivery of CBT4CBT in the Black church—an evidence-based, web-based intervention, shown to decrease the use of cocaine, alcohol, marijuana, and opioids in the clinical setting—may thereby attract, increase, and retain participation of BSD in evidence-based treatment, by minimizing some of the barriers experienced by a group with lower rates of accessing traditional forms of care. Academic collaboration with community partners, comprised of community activists, Black ministers and leaders, along with data obtained from community stakeholders and BSD, will prove useful in determining how this technology, CBT4CBT may be optimally integrated in the Black church setting. Aims for this study are to: (1) Engage key stakeholders in the Black community and clergy in Black churches in order to: (a) identify community and cultural factors related to BSD that might increase or decrease perceptions of stigma; (b) identify community/church attitudes/biases that might impact a BSD's likelihood of engaging with treatment; and (c) identify spiritual and religious practices or beliefs that might increase the acceptability of using a web-based intervention within the Black church; (2) Identify perceived barriers to help seeking and treatment engagement among BSD with an emphasis on stigma, while exploring attitudes and experiences associated with spirituality, religion, and the Black church, which might indicate a willingness to access treatment connected with the Black church; and (3) Facilitate the development of a community and BSD-vetted, web-based intervention to decrease BSD substance use and to increase the likely suitability of the intervention by iteratively bringing together community and BSD informants' perceptions on how best to achieve this goal.

## **W13. EFFICACY OF VORTIOXETINE IN WORKING PATIENTS WITH GENERALIZED ANXIETY DISORDER**

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**Abstract:** Objective: Vortioxetine is an approved antidepressant with a multimodal mechanism of action that has demonstrated positive effects on anxiety symptoms in patients with generalized anxiety disorder (GAD). The observed antidepressant effect of vortioxetine has been shown to be particularly high in working patients. As many patients with GAD are working, this post-hoc analysis aimed to examine the effect of vortioxetine (5-10 mg/day) on measures of anxiety, quality of life and global functioning in working GAD patients. Only GAD studies where vortioxetine met primary endpoint were selected for this analysis; one 8-week study in acute GAD (NCT00744627), and one relapse prevention study up to 56 weeks (NCT00788034).

Methods: In NCT00744627, patients with GAD (N=301) were randomized 1:1 to treatment with vortioxetine 5 mg or placebo. Efficacy was assessed by response (50% reduction in Hamilton Anxiety Rating Scale (HAM-A) total score, remission (Clinical Global Impression – Severity scale  $\leq 2$ ), and global functioning (Sheehan Disability Scale total score (SDS)), and quality of life (SF-36 social functioning subscore). In NCT00788034, patients with GAD (N = 687) were treated open-label with vortioxetine 5 or 10 mg for 20 weeks after which patients in remission were randomized 1:1 to fixed dose 5 or 10 mg or placebo for at least 24 weeks. The primary endpoint was time to relapse; quality of life and global functioning were also evaluated. Analyses were completed in individuals reporting to be working/taking an education at study entry and included in the full analysis set. Additionally, outcomes as a function of workplace position were analyzed. All analyses were made versus placebo.

Results: In NCT00744627, there was a greater proportion of responders versus placebo (odds ratio [OR] = 2.81;  $p < 0.002$ ) according to HAM-A in working patients compared to overall study population (OR = 2.39; ( $p < 0.001$ ), as well as remitters according to CGI-S (OR = 2.14;  $p < 0.03$  vs. OR = 1.88;  $p < 0.02$ ). The effect was greatest in patients with a managerial position in terms of response (OR = 3.5;  $p < 0.01$ ) and patients with an associate professional position for remission (OR=11.9;  $p < 0.01$ ). A greater effect in working patients with a managerial position was also observed on SDS and SF-36. In NCT00788034, working patients randomized to placebo were significantly more likely to relapse than those randomized to vortioxetine (hazard ratio 2.9;  $p < 0.000$ ) while the hazard ratio for the total study population was 2.7 ( $p < 0.000$ ). A greater effect was also observed in working patients with GAD on SDS social functioning score and SF-36 general health perception.

Conclusions: Results of these post-hoc analyses indicate that the beneficial effects of vortioxetine on clinician-rated and patient-reported measures of anxiety and overall functioning are greater in adults with GAD who are currently working and/or engaged in educational pursuits compared to the overall study population.

#### **W14. EXTENDED-RELEASE GUANFACINE FOR THE TREATMENT OF HYPERACTIVITY IN CHILDREN WITH AUTISM SPECTRUM DISORDER: AN ANALYSIS OF SECONDARY OUTCOME MEASURES**

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**Abstract:** Extended-Release Guanfacine for the Treatment of Hyperactivity in Children with Autism Spectrum Disorder: An Analysis of Secondary Outcome Measures

**Objectives:** Extended release guanfacine (GEXR) is approved for the treatment of children with attention-deficit hyperactivity disorder (ADHD). In a prior report, we showed that GEXR is safe and effective for children with autism spectrum disorder (ASD) accompanied by ADHD symptoms. Guanfacine is also frequently used to treat noncompliance, repetitive behavior, and anxiety in children with ASD, though these outcomes have not been carefully evaluated. Here, we examine the impact of GEXR on the Home Situation Questionnaire (noncompliance), the Anxiety scale of the Child and Adolescent Symptom Inventory, and the Children's Yale Brown Obsessive-Compulsive Scale for ASD that were collected in our multisite trial.

**Methods:** This was a five-site study in which 62 subjects (53 boys, 9 girls; mean age 8.5 + 2.25 years) were randomly assigned to GEXR (n=30) or placebo (n=32) for 8 weeks. The diagnosis of ASD was based on clinical assessment and supported by the Social Communication Questionnaire and the Autism Diagnostic Observational Schedule. Wilcoxon Rank Sum tests were used to compare percent change by treatment group and validated with ANCOVA models.

**Results:** The guanfacine group showed median declines of 47%, 25% and 13% in the Home Situation Questionnaire (HSQ), the Anxiety scale of the Child and Adolescent Symptom Inventory (CASI-Anxiety), and Children's Yale Brown Obsessive-Compulsive Scale for ASD (CYBOCS-ASD), respectively. By contrast, in the placebo-group, there were declines of 17%, 20% and 0% in the HSQ, CASI-Anxiety and CYBOCS-ASD, respectively (p= 0.02, 0.42 and 0.01).

**Conclusions:** In addition to improving hyperactivity in children with ASD, GEXR also appears to reduce symptoms of non-compliance and repetitive behavior. There were no significant effects on symptoms of anxiety, as measured by the CASI-Anxiety scale.

## **W15. NEUROINFLAMMATORY SIGNATURE OF TREATMENT RESPONSE TO KETAMINE IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION**

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**Abstract:** Background: Neuroinflammation—the inflammatory response representing maladaptive communication between neurons and the immune system—is increasingly recognized as essential to the pathology of neuropsychiatric disorders such as depression. The neuroinflammatory response involves not just inflammation in the CNS; there is complex bidirectional communication between the peripheral blood and the brain such that peripheral markers of immune activation may reflect central pathology. Although peripheral blood from patients may be obtained relatively easily, neural tissue is more difficult, and the initiating and perpetuating factors driving maladaptive neuroinflammation remain unclear.

Ketamine is a rapidly acting antidepressant that may be used as a probe to understand the pathology of anxious depression. In rodent models and a few human studies, response to ketamine has been associated with immune alterations in the peripheral blood (such as decreases in the proinflammatory cytokine IL-6). However, the neuroinflammatory response pre- and post-ketamine remains poorly studied.

The goal of the research currently underway is to better define the neuroinflammatory signature of depression using treatment response to ketamine, by 1) direct analysis of patient serum and

peripheral blood monocytes, and 2) examining the interaction between peripheral blood and induced pluripotent stem cell-derived neurons from healthy or depressed patients.

**Methods:** In an ongoing study examining biomarkers of treatment response to ketamine, 10 patients with treatment-resistant depression have undergone extensive phenotyping, including neuroimaging. Blood, serum, and fibroblasts for iPSC-neuron derivation from these patients have been collected and will be used in this study. Serum will be analyzed by multiplex immunoassay for a panel of cytokines and inflammatory markers. Peripheral blood monocytes (PBMC) will be phenotyped by flow cytometry and bioenergetics. In addition, serum or PBMC from these patients will be applied to iPSC-derived neurons, and neuronal activity phenotyped by multi-electrode recording, calcium imaging, and synaptic outgrowth.

**Results:** This project is ongoing; results will be presented at the meeting.

**Conclusion:** Results of this study will shed light on the neuroinflammatory pathology of depression and may help predict treatment response to ketamine.

## **W16. A STUDY OF METABOLIC DISTURBANCE IN ADOLESCENT PATIENTS WITH BIPOLAR DISORDER**

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**Abstract:** Background: Obesity and the metabolic syndrome are common in patients with bipolar disorder (BD). Previous studies indicate that metabolic syndrome and BD are intrinsically linked with convergent and bidirectional relationship (1,2). The association between early-onset BD and metabolic disturbance is poorly understood due to previous studies usually included only adult bipolar patients. This study aims to investigate the prevalence of metabolic disturbance in early-onset BD. Methods: Metabolic data [BMI, Triglyceride (TG) and High Density Lipid (HDL) Cholesterol, fasting blood sugar (FBS), and Systolic & Diastolic blood pressure (SBP, DBP)] from 140 children and adolescents (mean age  $\pm$  SD, 15.1  $\pm$  1.7 yr., 53% males) admitted to an acute psychiatric inpatient unit and meeting DSMIV criteria for a primary diagnosis of BD were examined in the current study. Presence of MS was defined by International Diabetes Federation (IDF) criteria and required at least 3 of the following 5 components: a) BMI>90th% for age and sex; b) SBP>130 or DBP>85, or on treatment for hypertension; c) FBS>100 or previously diagnosed type 2 Diabetes; d) TG> 150 or on treatment for elevated TG; and/or e) if age>16, HDL cholesterol<40 in boys or <50 mg in girls. The pediatric bipolar sample was then compared to a historical control group of age and sex matched children and adolescents without BD reported in the NHANES 1999–2000 study. Results: The pediatric BP inpatient group was more than twice as likely (14%) to meet criteria for MS in comparison to the historical control group (6.7%) of children and adolescents without BD [adjusted OR = 2.33(1.37-4.0)  $p$ <0.005]. The pediatric BP group (25%) also had a 2-fold greater risk for a BMI >90th% than the control group (11.8%) [adjusted OR = 2.49(1.62-3.82),  $p$ <.001] as well as a significantly greater rate of elevated BP (17%) than the control group (8%) [adjusted OR = 1.82 (1.05-3.13),  $p$ < 0.05]. Although there was no gender difference detected in co-occurrence of MS with BD, the boys with BD (41.4%) were significantly more likely to have an elevated BP than the girls with BD (23.2%) in the current study [adjusted OR = 0.24 (0.08-0.69,  $p$  = 0.005]. Conclusions: Compared with the general adolescent population the prevalence of MS was significantly higher in adolescent patients with BD. These findings supported that relative risk of metabolic disturbance occurs as early as in adolescent patients with BD. It indicates the understanding the effects of abnormal metabolic factors on early-

onset BD allows for understanding the development of BD and advancing a more rational, personalized preventive and therapeutic approach for BD.

#### **W17. COURSE OF TWO COMMON ADVERSE EVENTS IN ARIPIPRAZOLE ONCE-MONTHLY MAINTENANCE TREATMENT OF BIPOLAR I DISORDER DURING A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY**

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**Abstract:** Background: Aripiprazole Once-Monthly 400 mg (AOM 400) is an atypical long-acting injectable antipsychotic for the treatment of schizophrenia. The safety profile of AOM 400 in patients with schizophrenia is well-characterized and is similar to the profile of oral formulations of aripiprazole in patients with Bipolar I Disorder (BP-I), with akathisia and increased weight being the most frequent AEs. Additionally, the use of AOM 400 in the treatment of BP-I has recently been reported [1]. We further characterize the akathisia and weight gain reported in this study (NCT01567527) during more than 1 year of exposure to AOM 400 among patients with BP-I stabilized on oral aripiprazole and subsequently switched to AOM 400.

Methods: This double-blind, withdrawal study included patients aged 18-65 years diagnosed with BP-I (DSM-IV-TR). Treatments comprised cross-titration to oral aripiprazole (if necessary), stabilization on oral aripiprazole (2-8 weeks), then on AOM 400 (12-28 weeks), followed by 1:1 randomization of patients who met stabilization criteria to a 52-week, placebo-controlled withdrawal phase (maintenance treatment).

Results: Of 731 patients enrolled, 720 patients received at least one dose of aripiprazole, oral or oral+intragluteal injection. Of those enrolled, 141/731 (19.3%) discontinued due to AEs: 33/466 (7.1%) during cross-titration; 63/632 (10.0%) during oral stabilization; 37/425 (8.7%) during AOM 400 stabilization; and a total of 8/266 (3.0%) after randomization - 7/133 (5.2%) receiving AOM 400 and 1/133 (0.8%) receiving placebo.

Among all aripiprazole-treated patients, the most common AEs were akathisia and weight gain, reported in 168/720 (23.3%) and 76/720 (10.6%), respectively. The median onset of akathisia was 20 days after first dose of [oral] aripiprazole, with a median duration of 29 days for the first occurrence, and with 21/168 (12.5%) of those reporting akathisia experiencing more than one episode. Of 39 new occurrences of akathisia after patients began AOM 400 treatment, 30 (76.9%) occurred in the first 3 months. Nevertheless, rates of discontinuation due to akathisia were minimal: 8 (1.3%) during oral stabilization, 2 (0.5%) during AOM 400 stabilization, and 2 (1.5%) during AOM 400 maintenance treatment.

The mean (SD) change in weight during the oral stabilization phase was 0.3 (2.6) kg. Among patients randomized to AOM 400, the mean (SD) weight gain from beginning AOM 400 stabilization to last visit was 2.4 (7.2) kg. AEs of weight gain usually began within the first 3 months of AOM 400 treatment. The mean weight gain relative to baseline was <3.0 kg at any visit and weight gain appeared to plateau after 36 weeks.



Conclusion: Among patients in this study, new reports of akathisia were less frequent once patients progressed to AOM 400 maintenance treatment than during oral stabilization. Weight gain stabilized during maintenance treatment with AOM 400. These findings suggest that akathisia and increased weight during AOM 400 treatment are manageable and support the use of AOM 400 as a well-tolerated maintenance treatment of BP-I.

## **W18. PATIENT SELECTION FOR LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTIC USE IN BIPOLAR DISORDER: AN EXPERT CONSENSUS SURVEY**

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**Abstract:** Background: Although several long-acting injectable antipsychotics (LAIs) have FDA indications for bipolar disorder (BD), data on LAIs are far more limited for BD than schizophrenia/schizoaffective disorder (SCZ), and LAIs are much less used in BD.

Objective: To systematically assess expert opinion on the most appropriate types of patients with BD/SCZ for treatment with an LAI.

Methods: A panel of 34 experts (81% of solicited survey respondents) completed a 50 question survey rating the appropriateness of LAIs in relation to patient- and treatment-related characteristics. Respondents received an honorarium and were blinded to the project sponsor. The survey assessed LAI recommendations with respect to: 1) appropriate patients; 2) initiating treatment; and 3) continuation/maintenance treatment. Responses were scored on a 9-point Likert scale. Chi-square distributions across 3 ranges (1–3, 4–6, 7–9) were used to characterize expert agreement. Confidence intervals of the mean ratings designated first-, second-, or third-line categorical ratings, with a lower limit boundary >6.5 for first line consensus. We describe expert recommendations on patient- and treatment-related factors most appropriate for LAI treatment.

Results: Similar to SCZ, experts endorsed LAI treatment (first- or high second-line) for patients with BD who have a history of >2 hospitalizations, are homeless/in unstable housing, have a history of violence or a suicide attempt, have poor insight, are young adults (18-25yrs), or have substance use disorder. Only a history of multiple hospitalizations and a homeless/unstable housing situation received first-line ratings for all types of patients with BD.

Concerning treatment history, BD and SCZ recommendations were generally consistent, but again with generally lower ratings and less consensus on options below high second-line for BD. LAIs were considered appropriate (first- or high second-line) for BD patients who prefer LAIs, have done well on an LAI in the past, have a history of suboptimal adherence to medications, frequently miss clinic appointments, have failed to respond (or shown only a partial response) to lithium or anticonvulsant mood stabilizers, have a predominant history of manic relapses, or have done well on oral antipsychotics in the past but have never been treated with an LAI.

Conclusions: Recommendations for the use of LAIs in BD mirrored those for SCZ, but options were not as strongly endorsed as for SCZ, with less consensus on options below high second-line. This highlights the need for more experience and research in this area.

Disclosure: Research sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S.

**W19. ARIPIPRAZOLE ONCE-MONTHLY MAINTENANCE TREATMENT OF BIPOLAR I DISORDER, A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY: EFFECTS ON TYPES OF RECURRENCE AND ON RECOVERY**

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**Abstract:** Aims. To evaluate the effect of Aripiprazole Once-Monthly 400mg (AOM 400) on recurrence of mood episodes (manic, depressive, or mixed type) in the maintenance treatment of Bipolar I Disorder (BP-I).

Methods. The study (NCT01567527) included outpatients aged 18-65 years who at enrollment fulfilled DSM-IV-TR criteria for BP-I and had a manic episode with a Young-Mania Rating Scale (YMRS) total score  $\geq 20$ . Patients stabilized on oral aripiprazole, then on AOM 400, began a 52-week double-blind, placebo-controlled randomized withdrawal phase. Study endpoint was recurrence of a mood episode defined by criteria that included hospitalization, mania and depression scale scores, Clinical Global Impression score for BP-I severity, disease or clinical worsening, discontinuation for lack of efficacy, or active suicidality. Patients were considered in recovery if mania and depression scale scores were  $\leq 12$  for 8 consecutive weeks. Time to recurrence was analyzed using a log-rank test and recovery rates using Cochran-Mantel-Maenszel test.

Results. Two-hundred-and-sixty-six patients were randomized 1:1 to AOM 400 or placebo. Compared with placebo, AOM 400 significantly delayed time to recurrence of mood episodes ( $p < 0.0001$ ), reduced proportion of patients with recurrence ( $p < 0.0001$ , driven by fewer manic recurrences), and delayed time to hospitalization ( $p = 0.0002$ ). Recurrence of depressive episodes did not differ between treatments. Significantly more AOM 400 than placebo-treated patients met criteria for recovery (65% vs 50%,  $p = 0.012$ ).

Conclusions. For BP-I patients presenting with a manic episode, AOM 400 was superior to placebo in preventing recurrence of any mood episode, especially manic, during 52 weeks of treatment.

**W20. OPEN BOARD**

**W21. USE OF RECOMMENDED THERAPIES FOLLOWING A NEW ANXIETY DIAGNOSIS IN CHILDREN AND ADOLESCENTS**

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**Abstract:** Background: Psychotherapy, particularly cognitive behavioral therapy (CBT), and SSRI antidepressants are recommended treatments for pediatric anxiety.(1) Anxiety severity and co-morbidities influence the initial treatment choice; initiating with psychotherapy is recommended for mild severity.(1) The Child-Adolescent Anxiety Multimodal Study, a randomized controlled trial of children with moderate/severe separation anxiety disorder, generalized anxiety disorder, or social phobia (published in 2008) found that the combination of sertraline (an SSRI) and CBT resulted in greater improvement than sertraline or CBT alone; active treatments fared better than placebo.(2) It remains unknown how often combination therapy is utilized in pediatric anxiety and how often pediatric anxiety remains untreated.

Objective: To describe SSRI and psychotherapy initiation in children and adolescents shortly after their first anxiety diagnosis, and to examine variation in treatment type by year, provider type, and patient characteristics.

Methods: We identified children and adolescents (3-17 years) at their first recorded anxiety diagnosis corresponding to DSM-5 anxiety disorders, OCD, and PTSD (inpatient/outpatient ICD-9-CM code) from 2005-2014 in MarketScan Commercial Claims and Encounters database. We restricted our sample to children with continuous insurance enrollment, no psychotherapy, and no SSRI prescription in the year prior. We examined whether each child initiated with combination therapy (SSRI+psychotherapy), SSRI alone, psychotherapy alone, or neither SSRI nor psychotherapy (no therapy) in the 30 days after the first anxiety diagnosis. We defined SSRI use with records of dispensed prescriptions and psychotherapy with billed psychotherapy CPT codes.

Results: We identified 245,774 children and adolescents with a new anxiety diagnosis (median age=12 years, 55% diagnosed with unspecified anxiety, 30% with a psychiatric co-morbidity). In the 30 days after the first anxiety diagnosis, 4% initiated combination therapy, 9% SSRI alone, 38% psychotherapy alone, and 49% no therapy. Extending to 90 days after the first anxiety diagnosis, 41% had received no therapy. From 2005 to 2014 the proportion initiating with combination therapy remained stable (4%) while the proportion initiating with SSRI alone increased (6% to 10%), psychotherapy alone decreased (44% to 33%), and no therapy increased (46% to 53%).

Combination therapy was more common in children first diagnosed with agoraphobia (12%), social phobia (8%), or OCD (8%) and least common in children with selective mutism (1%). Few children first diagnosed by a pediatrician or family practice provider started with combination therapy (2% and 3%, respectively) and psychotherapy alone (8% and 7%) with higher use of SSRI alone (13% and 25%); 12% of children diagnosed by a psychiatrist initiated combination therapy. In adjusted analyses, younger age, diagnosis from a pediatrician/family practice provider, and no co-morbid depression were strong predictors of receiving no therapy while older age, OCD, panic disorder, diagnosis from a psychiatrist, and parent SSRI use were predictors of combination therapy.

Conclusions: We saw few children and adolescents initiate combination therapy following a first anxiety diagnosis; however, our study does not restrict by anxiety disorder or severity. The approximately half of children who do not receive either an SSRI or psychotherapy shortly after being diagnosed with anxiety may represent children with less severe anxiety, managing symptoms through other means, or referred for further follow-up, but this could include children with suboptimal/unmanaged anxiety.

## **W22. ARE SELF-REPORT SCALES AS EFFECTIVE AS CLINICIAN RATING SCALES IN MEASURING TREATMENT RESPONSE IN ROUTINE CLINICAL PRACTICE?**

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**Abstract:** Objective: Recent treatment guidelines have suggested that outcome should be measured in routine clinical practice. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, we compared three self-report scales of depressive symptoms and the two most widely used clinician administered scales in treatment studies in their sensitivity to change and evaluation of treatment response in depressed patients treated in routine practice.

Methods: At baseline and 4-month follow-up 153 depressed outpatients with DSM-IV MDD completed the Clinically Useful Depression Outcome Scale (CUDOS), Quick Inventory of Depressive Symptomatology—Self-report version (QIDS-SR), and Patient Health Questionnaire (PHQ-9). The patients were rated on the 17-item Hamilton Depression Rating Scale (HAMD) and Montgomery-Asberg Depression Rating Scale (MADRS). On each scale treatment response was defined as a 50% or greater reduction in scores from baseline.

Results: While there were some differences in the percentage of patients considered to be responders on the different scales, a large effect size was found for each scale, with little variability amongst the scales. The level of agreement between the three self-report scales and the clinician rating scales was approximately the same.

Discussion: When measuring outcome in clinical practice the magnitude of change in depressive symptoms is as great on self-report scales as on clinician rating scales.

## **W23. EXPANDING THE BRIEF ASSESSMENT OF COGNITION (BAC-APP) FOR USE IN SCREENING FOR MCI DUE TO AD**

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**Abstract:** Background: The Brief Assessment of Cognition in Schizophrenia (BACS) is a pen-and-paper cognitive assessment tool that has been used in hundreds of research studies and clinical trials. A tablet-based version of the BACS called the BAC App has been developed to allow standardized presentation of task instructions and stimuli, audio-recording of subject responses, and automatized scoring and data management. In order to extend use of the BAC App for screening and early detection of Mild Cognitive Impairment due to Alzheimer's disease (MCI-AD), we sought to incorporate additional tests of episodic verbal memory and visuospatial working memory into the BAC App.

**Methods:** The design and implementation of new BAC App measures is presented in conjunction with validation data indicating the equivalence of traditional pen and paper BACS and the BAC App in a study of 48 patients with schizophrenia and 50 healthy controls. Participants were recruited from three academic sites including the University of California-San Diego, the University of Miami - Miller School of Medicine, and the University of South Carolina. All participants were assessed with the standard pen-and-paper BACS and the BAC App.

**Results:** Distributions of standardized composite scores for the tablet-based BAC App and the pen-and-paper BACS were indistinguishable in both schizophrenia patients and healthy controls. Between-methods mean differences were not statistically significant. The discrimination between patients and controls was similarly robust with the BAC App ( $d=1.34$ ) and the BACS ( $d=1.24$ ). Additional verbal memory tests were incorporated to increase sensitivity to early deficits in episodic memory associated with MCI-AD. Novel verbal assessments include 1) delayed free recall 2) delayed recognition 3) delayed cued recall 4) delayed forced choice recognition. In addition, a novel visuospatial working memory task was implemented in which subjects are required to remember the placement of increasingly longer sequences of objects presented on a grid.

**Discussion:** The tablet-based BAC App generates results consistent with the traditional pen-and-paper BACS. Inclusion of additional measures of episodic memory and visuospatial working memory will increase the utility of the measure for use in early MCI-AD.

#### **W24. SAGE-217, A NOVEL POSITIVE ALLOSTERIC MODULATOR OF SYNAPTIC AND EXTRASYNAPTIC GABA-A RECEPTORS: PHASE 1 SINGLE- AND MULTIPLE-ASCENDING DOSE RESULTS**

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*<sup>1</sup>Sage Therapeutics, <sup>2</sup>2b Analytics*

**Abstract:** Background: Allopregnanolone is a neuroactive steroid (NAS) and a positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors. An earlier, proprietary, aqueous formulation of allopregnanolone (SAGE-547 Injection) showed encouraging signals of activity in subjects with multiple indications associated with a GABA-related etiology, including postpartum depression, essential tremor, and super-refractory status epilepticus. SAGE-217 Oral Solution is a second-generation NAS, with a mechanism of action similar to allopregnanolone, optimized for once-daily oral dosing.

**Methods:** These Phase 1, double-blind, placebo-controlled, single- (SAD) and multiple-ascending dose (MAD) studies enrolled a total of 108 healthy volunteers. In the SAD study, 72 subjects were randomized 6:2 to a single dose of SAGE-217 or placebo. Dosing was escalated from 0.25 mg to 66 mg across 9 cohorts. In the MAD study, 36 subjects were randomized 9:3 and received SAGE-217 (15, 30, or 35 mg) or placebo once daily in the morning for 7 days. After a washout period, subjects in the 30 mg cohort returned for 7 days of evening dosing. In both studies, the maximum tolerated dose (MTD) was determined based on a predefined Modified Observers Assessment of Awareness/Sedation (MOAA/S) stopping criterion, and electroencephalogram (EEG) recordings assessed electrical activity in the brain as a surrogate for target engagement.

Results: In both studies, SAGE-217 was well tolerated and no serious adverse events were reported. Rates of moderate to deep sedation (MOAA/S <3) were comparable with placebo until the MTD was reached. Pharmacokinetics (PK) results supported once daily administration; SAGE-217 was orally bioavailable with a half-life of 16-21 hours and a Tmax of approx. 1 hour. The SAD MTD was determined to be 55 mg daily, and EEG recordings suggested target engagement at doses below the MTD. The MAD MTD was 30 mg daily. SAGE-217 produced concentration-dependent pharmacodynamic (PD) effects as measured by elevations of beta-band EEG at all doses tested, and the effect was observed without diminution after each administration over the 7-day dosing period.

Conclusions: SAGE-217 was generally well tolerated, had PK supportive of once daily administration, and PD effects suggesting target engagement, which supports further development as a potential therapy for multiple indications related to GABA dysfunction. A Phase 2 clinical program has been initiated.

## **W25. SAGE-547 AND SAGE-217: NOVEL POSITIVE ALLOSTERIC MODULATORS OF SYNAPTIC AND EXTRASYNAPTIC GABA-A RECEPTORS BEING INVESTIGATED IN THE TREATMENT OF MOOD DISORDERS**

*Stephen Kanesh<sup>1</sup>, Helen Colquhoun<sup>1</sup>, James Doherty<sup>1</sup>, Shane Raines<sup>2</sup>, Ethan Hoffmann<sup>1</sup>, David Rubinow<sup>3</sup>, Samantha Meltzer-Brody<sup>4</sup>, A.J. Robichaud<sup>1</sup>*

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**Abstract:** GABA is the primary inhibitory neurotransmitter in the brain and binds to ligand-gated chloride ion channels (GABAA receptors) and G protein-coupled receptors (GABAB receptors). GABAA receptors are present both in the synapse as well as extrasynaptically, and their function can be enhanced by positive allosteric modulators (PAMs) that increase receptor efficacy and/or potency. Nonclinical and clinical evidence suggest the role of GABAergic dysfunction in a variety of disease states, including mood disorders such as postpartum depression (PPD) and major depressive disorder (MDD). In PPD, evidence indicates that rapid, post-childbirth decreases in levels of the endogenous neuroactive steroid (NAS) allopregnanolone, the predominant metabolite of progesterone and a PAM of GABAA receptors, may trigger PPD. In MDD, low GABA and allopregnanolone levels have been found in the brain, cerebrospinal fluid, and plasma of depressed patients, and multiple antidepressant agents have been shown to elevate allopregnanolone levels in animal models and in depressed patients.

SAGE-547 Injection (brexanolone, USAN) is a proprietary formulation of allopregnanolone. The safety, tolerability, pharmacokinetics (PK), and efficacy of SAGE-547 were initially evaluated in an open-label, proof-of-concept study that supported further investigation of SAGE-547 for severe PPD. A subsequent double-blind, randomized, placebo-controlled, Phase 2 study in 21 women with severe PPD showed SAGE-547 provided statistically significant and clinically meaningful reductions in 17-item Hamilton Rating Scale for Depression (HAM-D) total score at 24 hours (p=0.006) post infusion start and continuing through the primary endpoint of 60 hours (p=0.008) with reduction sustained at 30 days (p=0.01), relative to placebo. SAGE-547 was generally well tolerated.

SAGE-217 Oral Solution is a next-generation NAS with similar pharmacology to allopregnanolone and a PK profile optimized for once daily oral administration. SAGE-217 was investigated in Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) studies. In the SAD study, 72 healthy volunteers were administered SAGE-217 at doses between 0.25 and 66 mg in 9 double-blind, placebo-controlled cohorts (randomized 6:2). In the MAD study with 36 healthy volunteers, 3 double-blind, placebo-controlled cohorts (randomized 9:3) received morning doses of 15 mg, 30, and 35 mg over 7 days. The 30 mg cohort was also dosed in the evening for another 7 days.

SAGE-217 was generally well tolerated in the SAD and MAD trials. Doses were escalated until the maximum tolerated dose (MTD) was achieved based on pre-specified stopping criteria related to sedation. Electroencephalogram recording was used to assess electrical activity as a surrogate for target engagement (GABAA receptor modulation) and suggested evidence of target engagement starting at the lowest dose. The PK profile obtained in the SAD/MAD studies with SAGE-217 was consistent with once daily, oral dosing, displaying dose linearity over the multiple-dose range studied (15-35 mg) and a half-life ranging from 16-21 hours.

To date, results from clinical trials with SAGE-547 and SAGE-217 support continued development as potential therapies for mood disorders. Ongoing trials include a pivotal study with SAGE-547 in PPD, as well as Phase 2 studies of SAGE-217 in PPD and MDD.

## **W26. EFFICACY AND SAFETY OF INITIALLY INTRAMUSCULAR INJECTION SCOPOLAMINE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL**

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*Beijing Anding Hospital, Capital Medical University*

**Abstract:** Context: Previous studies showed that the intravenous administration of scopolamine produces antidepressant effects, however, the effects of add-on scopolamine to antidepressants have not been examined.

Objective: To determine if initial scopolamine with escitalopram produce rapid antidepressant effects.

Methods/Design: This study is a randomized, double-blind, placebo-controlled clinical trial. Sixty-six outpatients (ages 18–45) with severe major depressive disorder (MDD) (17-item Hamilton Rating Scale for Depression total score greater than or equal to 20) are enrolled from Beijing Anding Hospital. All participants receive oral escitalopram 10 mg/d throughout the total of 4 weeks treatment. Meanwhile, they are randomized equally to one of three add-on treatment arms during the first three days: (1) intramuscular injection (i.m.) with saline (1 ml) at 9 am and 3 pm per day; (2) scopolamine (0.3 mg in 1ml saline, i.m.) at 9 am and saline (1 ml, i.m.) at 3 pm per day; (3) scopolamine (0.3 mg in 1ml saline, i.m.) at 9 am and 3 pm per day, respectively. Depressive symptoms were measured using the Montgomery–Asberg Depression Rating Scale (MADRS) and 17-item Hamilton Rating Scale for Depression (HAM-D-17). Adverse psychopathological effects are measured with the Brief Psychiatric Rating Scale (BPRS)-positive symptoms, Young Mania Rating Scale (YMRS) and Clinician Administered Dissociative States Scale (CADSS). Patients were assessed at baseline, day 1, day 2, day 3, day 7, day 14 and day 28 by assessors masked to treatment assignments. Primary Outcome Measures: Change of 17-item Hamilton Depression Scale (HAM-D-17) total score

[Time Frame: From randomization to Week 2]; Secondary Outcome Measures: The proportion of subjects at endpoint with HAMD-17 $\leq$ 7; Safety Measures: The incidence and nature of overall adverse events; The incidence and nature of drug-related adverse events; Assessment of cognitive function change by PDQ-D5.

Primary outcome: Time to response ( $\geq$ 50% MADRS score reduction)

Secondary outcomes include self-reported depressive symptoms, physical and mental function, cognitive function.

## **W27. LOWER CONFIDENCE DIAGNOSTIC ASSIGNMENT IS ASSOCIATED WITH INCREASED NOISE IN EFFICACY RATINGS: AN INTERNATIONAL ANALYSIS**

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**Abstract:** Background. Excess variability in efficacy measure assessment is a potential contributor to clinical trial failure. Increasingly, pharmaceutical sponsors of psychiatric trials turn to remote independent raters for subject diagnostic confirmation in the belief this will improve detection of efficacy signal. We compared site raters' efficacy rating variance for subjects who did and did not receive external diagnostic confirmation.

Method. 4 IRB-approved international trials comprising 3 child and adult psychiatric indications from 3 separate sponsors were examined. Each trial included a site-independent remote assessment of subject diagnostic suitability following subjects' screening visits. To examine the potential utility of the independent diagnostic assessment in reducing variance, we compared the site-conducted efficacy scale ratings at screening for the subjects who were and were not externally deemed diagnostically acceptable. As the efficacy scales differed across studies, we compared each study individually.

Results: Of 3239 screening visits examined, 867 (27%) were judged by site-independent external review to be diagnostically questionable. For two of the trials, comprising the majority of subjects (N=2654), the variance of site-conducted screening efficacy ratings was significantly higher for the subjects independently deemed to be of low diagnostic confidence ( $p$ 's < .005 and .002, respectively). For the remaining two trials (comprising 585 patients), the results were not significant.

Conclusions: The results provide preliminary support for the value of independent diagnostic review as a means of potentially improving efficacy scale signal detection by site raters. The study provides an unusual opportunity to compare efficacy variance among subjects typically removed from outcome analyses.

## **W28. DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF KETAMINE THERAPY IN TREATMENT-RESISTANT DEPRESSION (TRD)**

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**Abstract:** Over the last two decades, a series of placebo-controlled studies has demonstrated the ability of intravenous ketamine (0.5 mg/Kg infusion), an N-Methyl-D-aspartate (NMDA) antagonist, to provide significant symptom amelioration in treatment-resistant depression (TRD) patients within a few hours, with symptoms typically returning within a period of days after discontinuation of the acute intervention. We wanted to investigate whether this is a dose-response effect of intravenous ketamine in TRD in the three days following the infusion. This was a six-site, double-blind, placebo-controlled study of the acute efficacy of intravenous ketamine or placebo added to ongoing, stable, and adequate antidepressant therapy (ADT) in the treatment of adults with TRD. The study was supported by NIMH through the RAPID contract. Following a washout period, 99 eligible subjects were randomly assigned to one of five arms in a 1:1:1:1:1 fashion: a single intravenous dose of ketamine 0.1 mg/kg (n=18), a single dose of ketamine 0.2 mg/kg (n=20), a single dose of ketamine 0.5 mg/kg (n=22), a single dose of ketamine 1.0 mg/kg (n=20), and a single dose of midazolam 0.045 mg/kg (active placebo) (n=19). The study assessments (HAM-D-6, MADRS, SDQ, PAS, SHAPS, CGI-S and CGI-I) were performed at Days 0, 1, 3 (endpoint), 5, 7, 14, and 30 to assess the safety and efficacy of all doses of ketamine compared to active placebo therapy in TRD patients. The overall group\*time interaction effect was significant, with both low- and high-doses of intravenous ketamine being superior to active placebo, in terms of the primary outcome measure, the HAM-D-6, as well as the SDQ. Most of the interaction effect was due to differences at Day 1. Our results challenge the view that only intravenous doses of 0.5 mg/kg or higher are effective in TRD.

## **W29. CLOZAPINE CLINICS AS MODELS FOR REVERSE INTEGRATED CARE DELIVERY TO REDUCE MEDICAL MORTALITY AND IMPROVE SAFETY IN PATIENTS WITH SERIOUS MENTAL ILLNESS**

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**Abstract:** Background: Psychiatric specialty clinics afford a unique opportunity to increase patient access to treatment and improve patient safety by bundling clinical services and integrating medical and psychiatric care. Clozapine is a medically high-risk medication that is underutilized in patients with serious psychotic disorders outside of academic medical centers. It lends itself to be used within a reverse integrated model of specialty care whereby medical services are brought to the psychiatric clinic.

Purpose and Methodology: The Massachusetts General Hospital (MGH) Schizophrenia Program has over 25 years of clinical experience with clozapine, organized around our clozapine clinic which is located in the Erich Lindemann Mental Health Center, a community mental health center in downtown Boston. The goal of the clinic is to expedite access to clozapine, promote its safe use, and develop a system of care to track psychiatric and medical outcomes. It also serves as a teaching clinic to train the next generation of psychiatrists in the optimal use of clozapine. Our presentation describes the evolution of our clinic, its critical

components, successes, and lessons learned in our efforts to improve medical care for psychiatric patients.

**Results:** We implemented an annual health screening for all patients to introduce medical prevention principles including metabolic monitoring, and we developed a patient registry to make possible population-based management. In 2016, our clozapine clinic consisted of 192 patients of which 49% completed the full annual health screening. 65-70% received guideline concordant metabolic monitoring. We developed a chronic disease management program to address cardiovascular risk factors. Since cancer has emerged as a major cause of death for this cohort, we developed a partnership with the MGH Cancer Center to streamline access to cancer care and promote co-management between psychiatry and oncology.

**Conclusion and Importance:** Our clozapine clinic has allowed us to offer timely care with clozapine to all patients in our own program, including our first-episode patients. We succeeded in implementing a metabolic monitoring program. Determining how to sustain our efforts and optimally coordinate medical care for patients identified via medical screening are critical next steps. Reverse integrated care using academic-community partnerships is a promising care delivery model for all patients with serious mental illness cared for in public and community psychiatric settings.

### **W30. ASSOCIATION OF BIPOLAR ILLNESS COURSE WITH FAMILY HISTORY OF ALCOHOLISM, BIPOLAR DISORDER, OR BOTH CONDITIONS IN FIRST DEGREE RELATIVES OF ADULTS WITH CO-OCCURRING BIPOLAR DISORDER AND ALCOHOL DEPENDENCE**

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**Abstract:** Background and Aims: Both alcohol dependence and bipolar disorder(s) are highly heritable conditions that commonly co-occur. Roughly half of all people with bipolar disorder will meet criteria for an alcohol use disorder at some point in their lives, and the lifetime prevalence of full alcohol dependence in individuals with Bipolar I disorder > 35%. Patterns of inheritance of the two conditions in affected individuals and their families are complex and poorly understood. The current study examined the relative associations of family history of either or both conditions on the course of bipolar illness in adults with co-occurring bipolar disorder and alcohol dependence.

**Methods:** Forty-three adults with Bipolar I or Bipolar II disorder who met DSM-IV criteria for current (past 30 days) alcohol dependence enrolled in a randomized controlled medication trial provided clinical histories of bipolar severity, alcoholism severity, and family history of both conditions. Associations between family history (+/- in first degree relatives) of alcohol dependence and/or bipolar disorder with dichotomous and continuous illness course variables for both conditions were assessed using chi-square and analysis of variance (ANOVA), respectively.

**Results:** Dichotomized family history of bipolar disorder was not associated with prior hospitalizations for mania, depression, or previous suicide attempt in this sample of bipolar alcoholics. In contrast, history of alcohol dependence in primary relatives was significantly associated with prior hospitalization for depression ( $p < .005$ ) and previous suicide attempt ( $p < .05$ ). Alcoholism severity variables did not differ significantly by family history of either alcohol dependence or bipolar disorder.

Conclusions: Results confirm that both bipolar disorder(s) and alcohol dependence are very common in first-degree relatives of individuals with comorbid bipolar disorder and alcohol dependence. Family history of alcohol dependence, but not of bipolar disorder, was associated with past severity of bipolar course of illness as measured by hospitalization for depression and by prior suicide attempts. These data suggest that clinical assessment of patients with comorbid bipolar disorder and alcohol dependence should include thorough screening of familial alcoholism.

### **W31. QUIT RATES OF DEPRESSED VS EUTHYMIC SMOKERS: IS THERE A DIFFERENCE?**

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**Abstract:** Introduction: Both depression and smoking are significant public health issues costing billions of dollars in direct and indirect costs annually. According to CDC the annual cost of smoking related illness is around \$ 300 Billion and according to research the cost of depression is around \$ 210 Billion per year. There is a significant correlation between mood symptoms and smoking. Data suggests that worsening of mood symptoms can lead to an increase in smoking. Data also suggests that depressed patients have difficulty in quitting smoking and even if they do, the chances of relapsing are high. We wanted to measure the impact of weekly group smoking cessation sessions on patients suffering from Major Depressive Disorder who wanted to quit smoking.

Methods: 225 adult smokers (age 18+) of at least 5 cigarettes per day who were interested in making a quit attempt in the next 30 days were recruited to participate in group smoking cessation treatment consisting of 6 weekly group sessions and including a 2-week supply of nicotine patches. Exhaled carbon monoxide (CO) and serum cotinine were measured at baseline. Participants were considered to have major depression disorder (MDD) if they had a score of >9 on the Patient Health Questionnaire-9 (PHQ-9). The Penn State Tobacco Dependence Index was used to measure tobacco dependence. Serum cotinine (ng/mL) was available on 199 participants. Chi-square tests, means (SD) and t-tests were used to measure the difference between those with MDD and those without for variables of interest. A multiple regression model was set up to determine predictors of tobacco dependence.

Results: 26.2% of our sample had MDD. Other demographic information included overall mean age of 48.5 (12.5), 60% female, 87% white, and 26% had a college degree or higher. Baseline cigarettes per day (CPD), CO, and cotinine was 17.6 (7.4), 21ppm (11.1) and 241ng/mL (124), respectively. There were no differences between the groups for any of these characteristics with the exception of tobacco dependence (13.4 for those with MDD v. 12.1 for those without,  $p=0.005$ ) and cotinine (211ng/mL for those with MDD v. 250ng/mL for those without,  $p=.06$ ). Those with MDD were slightly more likely to be quit at 4 weeks (45% without MDD versus 59% with MDD were quit,  $p=0.07$ ). After controlling for other factors, significant predictors of tobacco dependence were MDD ( $p=0.001$ ), CO ( $<0.001$ ), and confidence to quit at baseline ( $p=0.04$ ).

Conclusion: MDD is a significant predictor of tobacco dependence. We wanted to see if there was any difference in quit rates between tobacco dependent participants who were suffering from Major Depressive Disorder vs euthymic participants. In our cohort of 225 participants, 59 participants (26.2%) had MDD at the start of our study. Majority of our cohort were females

(60%) and white (87%). We utilized PHQ 9 and Penn State Tobacco Dependence Index to identify participants who had MDD and tobacco dependence. We found that the participants with MDD had a slightly higher quit rate than euthymic participants. This was contrary to previously published data. When we conducted statistical analysis, our cohort showed that MDD was a significant predictor of tobacco dependence in this population but there was no significant statistical difference in quit rates between the MDD and euthymic groups.

This interesting, albeit limited, finding should be replicated in a larger cohort. We would also like providers to be aware of how depression and tobacco dependence are co related, their impact on short and long term tobacco quit rates and our observation that depressed patient can quit smoking.

### **W32. ITI-333: A NOVEL MODULATOR OF SEROTONIN, DOPAMINE, AND MU OPIATE RECEPTORS FOR THE TREATMENT OF MOOD DISORDERS**

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*Intra-Cellular Therapies, Inc.*

**Abstract:** Background: A series of novel compounds has been discovered that interact with 5-HT<sub>2A</sub>, D<sub>1</sub> and mu opiate receptors. ITI-333, exemplifies this group, and possesses low nanomolar affinity for 5-HT<sub>2A</sub>, D<sub>1</sub> and mu opiate receptors with K<sub>i</sub> values of 8.3nM, 5.1nM and 11nM, respectively. The pharmacological profile of ITI-333 is reported here.

Methods: The pharmacological profile of ITI-333 was determined using in vitro receptor binding and cell-based functional assays and in vivo tests of functional activity at 5-HT<sub>2A</sub>, D<sub>2</sub>, and mu opiate receptors, including DOI-induced head twitch, morphine-induced hyperactivity, and blockade of morphine-induced analgesia in the mouse tail flick assay. To interrogate cellular signaling events involved in the actions of ITI-333, phosphoprotein levels (e.g, tyrosine hydroxylase and GluN2B) in key neurotransmitter pathways were assessed.

Results: ITI-333 is orally active with excellent metabolic stability in rodents. Oral administration of ITI-333 potently blocked DOI-induced head twitches in mice (EC<sub>50</sub> = 0.23mg/kg, p.o.) indicating strong functional activity in vivo as a 5-HT<sub>2A</sub> antagonist. ITI-333 did not alter presynaptic striatal dopamine D<sub>2</sub> mediated neurotransmission at doses tested, as indicated by a lack of effect on striatal tyrosine hydroxylase, the rate-limiting enzyme of dopamine synthesis. ITI-333 (0.3mg/kg, p.o.) potently antagonized morphine in vivo, blocking morphine-induced hyperactivity and morphine-induced analgesia in mice at dose levels comparable to its 5-HT<sub>2A</sub> receptor effects (i.e., 0.1mg/kg and above, p.o.).

Conclusion: Based on this novel pharmacological profile, including potent 5-HT<sub>2A</sub>, D<sub>1</sub> and mu opiate receptor interactions, ITI-333 is being developed for the treatment of mood disorders and opiate abuse, particularly in patients with co-morbid substance use disorders with symptoms of depression and/or anxiety.

### **W33. DESIGNING A RANDOMIZED PLACEBO CONTROLLED CROSS-OVER TRIAL INVESTIGATING NABILONE AS A TREATMENT FOR AGITATION IN PATIENTS WITH MODERATE-TO-SEVERE ALZHEIMER'S DISEASE**

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**Abstract:** Background: Current pharmacological management of agitation in Alzheimer's disease (AD) includes medications with modest benefits and high risk-profiles. Nabilone, a synthetic cannabinoid, has a distinct pharmacological profile, which may potentially treat agitation, while having benefits for weight and pain. Additionally, emerging evidence suggests that cannabinoids may have neuroprotective and anti-inflammatory effects. Such effects might reduce oxidative stress and brain cholesterol metabolism. We describe a clinical trial to investigate the safety and efficacy of nabilone in agitated patients with moderate-to-severe AD. Methods: This is a double-blind, cross-over randomized placebo controlled trial (RCT) comparing 6 weeks of nabilone (0.5-2mg) to 6 weeks of placebo, with a 1-week washout preceding each treatment phase. The recruitment goal is to randomize 40 patients. The primary outcome is agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI) based on previous trials. The secondary outcomes include behaviour (Neuropsychiatric Inventory (NPI)-NH), cognition (standardized Mini Mental Status Exam (sMMSE) and Severe Impairment Battery (SIB)) and global impression (Clinician's Global Impression of Change (CGI-C)). Exploratory outcomes include pain (Pain Assessment in Advanced AD (PAIN-AD)), nutritional status (Mini-Nutritional Assessment-Short Form (MNA-SF)), safety and investigation of potential biological targets including redox modulations, inflammation and cholesterol metabolism.

Results: This cross-over RCT will assess the therapeutic relevance of nabilone in the treatment of AD by investigating its efficacy in the treatment of agitation, pain and weight, while collecting double-blind information on safety.

Conclusions: If positive, the findings of this study will provide a rationale for the feasibility of a larger, multicentre trial. A safe and efficacious pharmacological intervention for agitation, with benefits on pain and weight loss in those with moderate-to-severe AD could increase quality-of-life, reduce caregiver stress and avoid unnecessary institutionalization and related increases in health-care costs.

#### W34. CHALLENGES IN THE TRANSLATION OF THE NEUROPSYCHIATRIC INVENTORY (NPI) INTO 74 LANGUAGES

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**Abstract:** Objectives. The Neuropsychiatric Inventory (NPI) was developed in US English to assess, through interviews with caregivers, ten behavioral disturbances occurring in dementia patients: A. Delusions, B. Hallucinations, C. Agitation/Aggression, D. Depression/Dysphoria, E. Anxiety, F. Elation/Euphoria, G. Apathy/Indifference, H. Disinhibition, I. Irritability/Lability, and J. Aberrant Motor Behavior. Two neurovegetative areas were added afterwards: K. Sleep, and L. Appetite and Eating Disorders. Screening questions assess the presence or absence of changes in behaviors in the patient. If the behavioral change is present, then, subquestions (n=7 to 9) are asked to evaluate behaviors in terms of frequency, severity,

and distress. The objective of this study was to present the challenges faced during the translation of the NPI-12 into 74 different languages representing ten language families.

Methods. The NPI was translated in most languages with a process including: 1) Concept definition with the developer 2) Forward/backward translation step; 3) Final reconciliation; 5) Clinician review; and 6) Proof-readings.

Results. The translation process did not reveal any cultural issues since most of the concepts assessed were cross-culturally relevant. The psychiatric terms (e.g., delusions, euphoria, etc.) were carefully translated with the clinician input in each country. When a literal translation was impossible, synonyms or periphrases were used. Most of the challenges identified were linked to the use of idiomatic/colloquial content, such as the use of “talk big” in subquestion 6 (Does the patient “talk big”) in section F, or the use of “flying off the handle” in subquestion 1 (Does the patient have a bad temper, flying “off the handle”...) in section I. In some languages, idiomatic expressions were available to express the same notions. However, in many languages either a synonym or a circumlocution was needed. Examples are presented.

Conclusions. A rigorous methodology was essential in producing NPI translations conceptually equivalent to the US English original.

### **W35. RELAPSE PREVENTION WITH LEVOMILNACIPRAN ER IN ADULTS WITH MAJOR DEPRESSIVE DISORDER: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY**

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**Abstract:** Background: Levomilnacipran extended-release (LVM-ER) is a serotonin and norepinephrine reuptake inhibitor approved for the treatment of major depressive disorder (MDD) in adults. The efficacy and safety of LVM-ER has been evaluated in 5 randomized, double-blind, placebo-controlled trials and 1 long-term open-label study. This withdrawal study was designed to evaluate the efficacy, safety, and tolerability of LVM-ER in the prevention of relapse in patients with MDD.

Methods: Patients in this study received 20 weeks of open-label treatment with LVM-ER 40, 80, or 120 mg/d (8 weeks of flexible-dose treatment followed by 12 weeks of stable dosing). Patients with a Montgomery-Åsberg Depression Rating Scale (MADRS) total score  $\leq 12$  from Week 8 through Week 20 of the open-label period were eligible to enter the 26-week randomized, double-blind, placebo-controlled withdrawal period. Patients were randomized to LVM-ER (continued at the same dosage) or placebo. The primary efficacy endpoint was time to first relapse, defined as a MADRS total score  $\geq 18$  or insufficient therapeutic response ( $\geq 2$ -point increase in Clinical Global Impressions-Severity score, suicide risk, or worsening of depression requiring medication switch or hospitalization). Standard safety assessments were applied, including adverse event (AE) reporting.

Results: In the double-blind intent-to-treat population (placebo, n=159; LVM-ER, n=165), patients who continued receiving LVM-ER had a significantly longer time to relapse ( $P < .05$ ) and lower risk of relapse than patients who were switched to placebo (hazard ratio, 0.56; 95% CI, 0.33-0.92). Crude relapse rates were 14.5% and 24.5% in the LVM-ER and placebo groups, respectively. Based on Kaplan-Meier estimates, approximately 25% of patients in the placebo group relapsed by Day 168; the corresponding estimate for LVM-ER was not available due to

the low relapse rate in this group. The incidence of treatment-emergent AEs (TEAEs) during the double-blind period was 58.8% in the LVM-ER group and 56.0% in the placebo group. TEAEs that occurred in  $\geq 5\%$  of LVM-ER-treated patients and at a higher incidence than placebo were headache (10.3% vs. 7.5%), upper respiratory tract infection (9.7% vs. 6.3%), nausea (7.9% vs. 3.1%), and nasopharyngitis (6.7% vs. 4.4%). Discontinuation due to AEs occurred in  $< 5\%$  of patients (LVM-ER, 3.0%; placebo, 1.3%); serious AEs occurred in  $< 2\%$  of patients (LVM-ER, 1.2%; placebo, 0.6%).

Conclusion: Among patients who responded to acute phase therapy with LVM-ER (40-120 mg/d), continuation phase therapy was both well-tolerated and significantly reduced the risk of relapse.

### **W36. DOES EARLY IMPROVEMENT WITH VILAZODONE PREDICT RESPONSE AND REMISSION IN PATIENTS WITH MDD?**

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**Abstract:** Background: APA treatment guidelines for major depressive disorder (MDD) indicate that adequate treatment duration (4-8 weeks) may be needed before concluding whether a patient is responsive to treatment. However, information about whether early symptom improvement with various antidepressants is predictive of subsequent response or remission may be useful so that patients can be properly advised about their medications and treated accordingly. Vilazodone (VLZ), which is approved at doses of 20-40 mg/d for the treatment of MDD in adults, has shown efficacy in 4 double-blind, placebo (PBO)-controlled trials (NCT00285376, NCT00683591, NCT01473381, NCT01473394), including significantly higher MADRS response rates at end of treatment compared to PBO ( $P < .05$ ). Post hoc analyses of data from these 4 trials (VLZ 40 mg/d, PBO) were conducted to evaluate whether early improvement with VLZ was predictive of later response or remission.

Methods: In all 4 MDD studies, VLZ 40 mg/d was titrated as follows: 10 mg/d (1 week); 20 mg/d (1 week); 40 mg/d (6-8 weeks). Early improvement, defined as  $\geq 30\%$  reduction from baseline in MADRS total score was analyzed at Week 2. Response (MADRS total score reduction  $\geq 50\%$ ) and remission (MADRS total score  $\leq 10$ ) were analyzed using Week 8 data from all 4 studies. Parameters for the predictor analysis included positive predictive value (PPV), sensitivity (SN), negative predictive value (NPV), and specificity (SP).

Results: At Week 2, all VLZ-treated patients were receiving 20 mg/d. The percentage of patients with early improvement was higher with VLZ (31.4%) than with PBO (25.5%). PPV analyses indicated that among early improvers, 60.3% and 69.7% of PBO- and VLZ-treated patients, respectively, were responders at Week 8; 48.1% and 57.1% were remitters at Week 8. However, SN analyses indicated that among Week 8 responders, only 47.7% and 48.9% of PBO- and VLZ-treated patients, respectively, were early improvers; among Week 8 remitters, 56.7% and 58.4% were early improvers. NPV analyses indicated that the majority of non-improvers at Week 2 were also nonresponders (PBO=77.3%, VLZ=66.6%) and nonremitters (PBO=87.4%, VLZ=81.3%) at Week 8. SP analyses indicated that most Week 8 nonresponders (PBO=83.1%, VLZ=82.7%) and nonremitters (PBO=83.1%, VLZ=80.5%) did not have early

improvement at Week 2. All predictor models for PBO and VLZ were statistically significant ( $P < .05$ ).

Conclusions: Pooled data from 4 MDD studies indicated that at Week 2, VLZ patients had higher rates of early improvement than PBO patients. The predictor model showed that only 50-60% of responders and remitters were early improvers, possibly because many VLZ-treated patients had not reached their optimal therapeutic dose by Week 2. Per FDA-approved recommendations, titration over several weeks to the maximum approved dose of VLZ 40 mg/d may be required in some MDD patients.

### **W37. ASSESSMENT IN WORK PRODUCTIVITY AND THE RELATIONSHIP WITH COGNITIVE SYMPTOMS (ATWORC): PRIMARY ANALYSIS FROM A CANADIAN OPEN-LABEL STUDY OF VORTIOXETINE IN FIRST TREATMENT AND SWITCH PATIENTS WITH MAJOR DEPRESSIVE DISORDER**

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**Abstract:** Objectives: Cognitive dysfunction is an important part of the clinical presentation of Major Depressive Disorder (MDD). However, few studies have assessed the relationship between cognitive dysfunction and workplace productivity. AtWoRC (Assessment in Work productivity and the Relationship with Cognitive symptoms in patients with MDD taking vortioxetine; NCT02332954) is an interventional, open-label, Canadian study designed to assess the association between cognitive symptoms and work productivity in gainfully employed patients with MDD treated with vortioxetine.

Methods: Patients diagnosed with MDD were prescribed vortioxetine and assessed over a total of 52 weeks at routine care visits that emulated a real-life setting. Patients were classified as having not been treated with another antidepressant (first treatment) or having inadequate response to one previous antidepressant (switch). The primary endpoint is partial correlation between changes in self-reported cognitive symptoms (20-item Perceived Deficits Questionnaire; PDQ-D-20) scores and self-reported work productivity loss (Work Limitations Questionnaire; WLQ) scores over 12 weeks of vortioxetine treatment. Additional assessments include changes in symptom and disease severity, functioning, pharmacoeconomics, as well as safety and tolerability. All analyses investigated both first treatment and switch patients.

Results: Data presented here are from the primary analysis at Week 12; the study is currently ongoing. As of November 2016, 196 eligible patients (97 first treatment, 99 switch) at 26 sites were enrolled, received at least one treatment dose, and attended at least one post-baseline study visit. Primary analysis at Week 12 indicated a significant correlation between patient reported PDQ-D-20 and WLQ productivity loss scores ( $r = 0.633$ ;  $p < 0.001$ ; full analysis set [FAS], observed cases [OC]). The correlation between PDQ-D-20 and WLQ productivity loss scores was comparable and significant in both first treatment ( $r = 0.671$ ;  $p < 0.001$ ; OC) and switch patients ( $r = 0.584$ ;  $p < 0.001$ ; OC). In addition, both first treatment and switch patients improved significantly from baseline in various mood, cognitive, and functional assessments



(eg, Quick Inventory of Depressive Symptomology–Self-Rated; Digit Symbol Substitution Test, Sheehan Disability Scale). At Week 12, rates of response for first treatment and switch patients were 69% and 61% respectively; rates of remission were 41% and 36% respectively. Safety and tolerability were consistent with the label information for vortioxetine.

Conclusions: Improvements in self-reported cognitive dysfunction were significantly associated with improvements in self-reported workplace productivity in Canadian patients with MDD, after 12 weeks of treatment with vortioxetine. Importantly, both first treatment and switch patients also demonstrated clinically relevant improvements in mood, cognitive function, overall functional outcomes, as well as rates of treatment response and disease remission from baseline to Week 12. These results are among the first to show a relationship between cognitive dysfunction in MDD and workplace productivity in a real-world setting.

### **W38. EXPLORATION OF THE INSULAR ROLE IN PSYCHOLOGICAL AND PHYSICAL PAIN IN ACUTE SUICIDALITY**

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**Abstract:** Objective: Growing evidence points to a significant role of abnormalities in the processing of both physical and psychological pain in suicide. We aim to study insular activity during social exclusion and its correlation with pain processing recent suicide attempters and suitable depressed and healthy controls.

Method: We exposed depressed adult patients within three days of a suicide attempt, patients with suicidal ideation, non-suicidal depressed patients, and healthy controls (N= 9-18) to social exclusion with the Cyberball game while undergoing functional magnetic resonance imaging scanning. We used complementary functional connectivity and region of interest (ROI) based approaches to explore the insula's role in social exclusion and its association with pain processing across the suicide risk spectrum.

Results: Despite no difference in functional connectivity among neural networks involving the insula, local neural activity in the insula showed an inverted U-shape curve with increasing suicide risk. Additionally, neural activity in the anterior insula correlated positively with clinical measures of depression severity or psychological pain; however, it correlated negatively with pressure pain threshold or suicidal ideation.

Conclusion: Our findings provide evidence of the intertwined neural processing of physical and psychological pain in acute suicidality.

### **W39. UCSD PERFORMANCE-BASED SKILL ASSESSMENT (UPSA): PSYCHOMETRIC EVALUATION OF THE COMMUNICATION AND FINANCIAL SKILL DOMAINS**

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**Abstract:** Background: The UCSD Performance-Based Skill Assessment (UPSA) is a performance-based measure of functional capacity commonly used in trials of persons with serious mental illness. The Phase 3 CONNECT study (Mahableshwarkar 2015), the first large-scale, double-blind study evaluating functional capacity in patients with MDD using the

domain UPSA-VIM (US sites) and 2 skill domain UPSA-B (non-US sites) analyzed as a composite score (Harvey 2016). The UPSA-B was used outside the US because the UPSA-VIM contains more information that requires cultural adaptation. One potential concern with this approach is the difference in the number and scoring of the skill domains on the two versions. This post hoc analysis examines the psychometric properties of the UPSA-B aligned which is composed of the two overlapping domains (Financial, Communication) from UPSA-VIM and UPSA-B.

Methods: A post hoc scoring adjustment was made to the UPSA-VIM Financial and Communication Skills domains to be consistent with the UPSA-B scoring, yielding the UPSA-B aligned score. Construct validity was examined via baseline correlation analyses (Spearman's  $r$ ) with cognitive (DSST, TMT-B) and clinical (WLQ, PDQ, MADRS) outcomes. Anchor- (CGI-I  $<2$ ) and distribution-based (0.5 SD) methods were used to establish a responder definition using data from the CONNECT study.

Results: A total of 528 subjects were included in this analysis. The mean baseline UPSA-B aligned score was 78.4 (SD=13.33). Moderate and significant baseline correlations were observed between the UPSA-B aligned and the DSST ( $r=0.31$ ,  $p<0.001$ ) and the TMT-B ( $r=0.36$ ,  $p<0.001$ ) and a small but significant correlation with the WLQ ( $-0.15$ ,  $p<0.05$ ). No correlation was observed with the MADRS ( $r=-0.03$ ) or PDQ ( $-0.05$ ). The responsiveness of the UPSA-B aligned was supported by a significantly greater mean change from baseline in subjects defined as responders than non-responders (6.3 vs. 4.3,  $p=0.0335$ ). The anchor- and distribution-based methods yielded estimates of 6.3 (mean change from baseline in responders) and 6.6 (0.5 SD), respectively. These results support a responder threshold of  $\geq 6$  points. In the CONNECT study, 51.4% of subjects treated with vortioxetine had a change from baseline meeting this criteria compared with 45.2% and 46.0% of subjects treated with placebo and duloxetine, respectively.

Conclusion: The psychometric properties UPSA-B aligned are similar to those of the UPSA composite score for construct validity and responsiveness.

#### **W40. A NOVEL USE OF THE GOAL ATTAINMENT SCALE AFTER CHANGE TO VORTIOXETINE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER**

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**Abstract:** Traditional methods of tracking the progress of patients undergoing treatment for major depressive disorder (MDD) rely on patient-reported outcomes (PROs) and clinician-reported outcomes (ClinROs). Here we describe a novel study of the real-world effectiveness of vortioxetine, an approved antidepressant. The study is designed to overcome many of these limitations by focusing on personalized patient goals by adapting the Goal Attainment Scale (GAS) for MDD. Although the GAS has long been used in clinical care and program assessment to evaluate patient progress and ensure alignment between clinician and patient on treatment objectives in other diseases, this is the first study to use the GAS as a primary endpoint within MDD to assess the effectiveness of antidepressant therapy.

Where traditional methods of evaluating treatment success in MDD do not fully account for outcomes that matter to patients, the GAS presents the opportunity to personalize the definition of treatment success for each MDD patient. By adapting the GAS to MDD, the patient's

personal goals and areas of personal concerns are taken into account, which can lead to more motivating treatment goals. In a move toward the personalization of treatment goals, 200 patients with MDD were surveyed to provide the patient perspective on the GAS scale and its implementation in the study.

In this phase 4 pragmatic clinical trial, patient-centric, real-world information will be collected from 120 MDD patients, and the effectiveness of vortioxetine on participants' goal achievement will be determined (ClinicalTrials.gov ID NCT02972632). The study will enroll adults in the United States who have been diagnosed with MDD and are currently being treated with an FDA-approved antidepressant, but are considering a switch in antidepressant medication because of inadequate response or tolerability issues. The decision to switch medication will be made in consultation with their physician. The primary objective of the study is to determine the proportion of participants who achieve significant improvement from baseline in their GAS score after 12 weeks of vortioxetine treatment. Enrollment is currently ongoing and the first patient was enrolled in January 2017.

This is the first study to use the GAS as a primary endpoint to quantitatively assess achievement of patient-centric outcomes in MDD that could otherwise be neglected when using traditional PROs and ClinROs as measures of clinical success. The GAS adapted for MDD establishes patient goals that are more personalized and may better reflect functional improvement from the patient's perspective. In addition to this study's goal of understanding the effectiveness of vortioxetine in a real-world setting, these findings could serve as a blueprint for a framework by which clinicians and MDD patients establish meaningful treatment goals and quantify the achievement of those goals in a real-world clinical practice.

#### **W41. VORTIOXETINE AND SUICIDAL IDEATION AND BEHAVIOR IN ADULTS WITH MAJOR DEPRESSIVE DISORDER**

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**Abstract:** Major depressive disorder (MDD) is one of the most important risk factors for suicide.<sup>1</sup> Further, an increased risk for suicidal behavior may be linked to antidepressant use, especially in children and adolescents.<sup>2</sup> Vortioxetine is an antidepressant with a novel multimodal mechanism of action that combines direct modulation of multiple serotonergic receptor activities and inhibition of the 5-HT transporter.<sup>3</sup> Here we present an analysis of data from registration trials for vortioxetine to better characterize the risks for suicidal ideation and behavior. Suicide-related events were evaluated in 2 pooled analyses of 7 and 10 short-term (6-8 wks), double-blind, controlled studies in MDD comparing vortioxetine (5, 10, 15 and 20 mg), placebo (PBO), and duloxetine (DLX) using the Columbia-Suicide Severity Rating Scale (C-SSRS) and assessing suicide-related treatment-emergent adverse events (TEAEs), respectively. A separate pooled analysis of 3 open-label studies assessed suicide-related events with long-term vortioxetine (2.5 to 20 mg) exposure up to 52 wks. The appearance of suicidal ideation and behavior, including completed suicides and suicide attempts, was measured using the C-SSRS, and suicidal behavior was categorically considered worse than suicidal ideation. Events that occurred any time before study drug administration in the initial double-blinded study (all prior history), between screening and randomization (baseline), and throughout the studies along with suicide-related TEAEs were reported.

At baseline, 14.7% of patients in the PBO group, 19.8%, 13%, 11.2%, and 13.7% in the 5, 10, 15 and 20 mg vortioxetine groups, respectively, and 13.2% in the DLX group reported any

suicidal ideation or behavior based on C-SSRS used in 7 of the short-term studies. These values did not vary throughout the short-term studies, with 17% of patients in the PBO group, 19.3%, 13.5%, 12.6%, and 15% in the 5, 10, 15 and 20 mg vortioxetine groups, respectively, and 11.3% in the DLX group reporting suicidal ideation or behavior. The proportions of patients who shifted from baseline C-SSRS categories of no suicidal ideation or behavior, suicidal ideation, or suicidal behavior to a worse category during the study were similar between treatment groups. The incidence of suicide-related TEAEs (suicidal ideation, intentional overdose, suicide attempt, intentional self-injury, self-injurious behavior) was low and similar between PBO (0.4%), vortioxetine (0.2%, 1%, 0.7%, and 0.7% for 5, 10, 15 and 20 mg), and DLX (0.7%) groups, with no dose-related increases observed for vortioxetine.

In the pooled analysis of open-label long-term studies evaluating flexible doses of vortioxetine, 28.3% and 13.3% of patients had prior histories of suicidal ideation and suicidal behavior, respectively. During the 52-wk treatment period, 9.8% and 0.2% of patients reported suicidal ideation and suicidal behavior, respectively, at any vortioxetine dose. Categorically, most patients shifted in a positive direction. Among patients with prior histories of either suicidal ideation or behavior, 78.5% and 80.2%, respectively, reported neither suicidal ideation nor behavior during the study and <1% from any category shifted to the worst category of suicidal behavior. There were no completed suicides in either of the studies.

Collectively, these data indicate that acute treatment with or long-term exposure to vortioxetine did not exacerbate the risk of suicidal ideation and behavior in MDD patients.

#### **W42. AN OPEN LABEL TRIAL OF DEXTROMETHORPHAN FOR DEPRESSION IN PSYCHIATRIC INPATIENTS**

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**Abstract:** Background: Depressive disorders represent a global public health concern. World Health Organization data indicate that unipolar depressive disorders alone account for 65.5 million disability-adjusted life years lost, and rank third among the leading causes of global disease burden. Currently approved medications for the management of depression offer only limited efficacy, and have a significant delay in onset of therapeutic effect. Ketamine and Nitrous Oxide, both NMDA receptor antagonists, offer fast-acting (hours-days) antidepressant effects, which make them attractive treatments in the armament against depression in general, but especially in venues of care where depression symptoms are severe, and quick relief could reduce care costs, longitudinal morbidity and mortality (like in an inpatient psychiatric setting), and could serve as new adjuncts to the current standard-of-care treatments for depression associated with Major Depressive Disorder and Bipolar Disorder (SSRIs, Lamotrigine, Atypical Antipsychotics, etc.).

Aims: Conduct a proof-of-concept study to investigate if the readily available and low-cost NMDA-receptor antagonist, Dextromethorphan, offers fast acting antidepressant effects like other promising drugs with similar primary mechanisms of action, like Ketamine.

Methods: Adults aged 18-65, who met DSM-IV criteria for a major depressive episode associated with a primary diagnosis of Major Depressive Disorder or Bipolar Disorder, and were hospitalized for depression, were eligible to participate in the study. Mood symptoms were assessed before and at several time points after 2 oral doses of 75mg of Dextromethorphan that were separated by 4 hours. Mood assessments were performed 2-4, 6-8, and 24-36 hours

after the initial dose and 1 week following the initial dose when possible during a follow-up assessment. Depression and anxiety symptoms were measured using the Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI-II), and the State Trait Anxiety Inventory Form Y1 (STAI), respectively. Change(s) from baseline MADRS, BDI, and STAI scores at the three post-dosing time points were analyzed using 1-way repeated measures analysis of variance (ANOVA).

Results: To date, four study participants (n=3 male, age range 23-38 years of age, all with a primary diagnosis of Major Depressive Disorder) have completed all inpatient procedures. A significant main effect of time was evident for all three measures: MADRS (mean change = -13.2,  $p<.05$ ), BDI (mean change = -19.8,  $p<.01$ ), STAI (mean change = -16.1,  $p<.05$ ). For each measure, changes were evident by 2-6 hours after the first dose of dextromethorphan and persisted through 24-36 hours after the second dose. No appreciable adverse events attributable to dextromethorphan have been reported to date.

Conclusions: Despite notable limitations including very small sample size and uncontrolled open label design, preliminary data from this ongoing proof-of-concept study suggest that Dextromethorphan may have rapid-acting antidepressant effects in the targeted population. Should these results extend through study completion, replication using a randomized, placebo-controlled design may be warranted.

#### **W43. COST-EFFECTIVENESS EVALUATION OF DEPRESSIVE AND COGNITIVE OUTCOMES OF VORTIOXETINE IN PATIENTS IN THE UNITED STATES WITH MAJOR DEPRESSIVE DISORDER SWITCHING FROM FIRST ANTIDEPRESSANT THERAPY**

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**Abstract:** Objective: To evaluate the impact of cognitive effects on the cost-effectiveness of vortioxetine versus levomilnacipran and vilazodone for the treatment of major depressive disorder (MDD; the 3 most recently approved agents for MDD by the US Food and Drug Administration) in patients with an inadequate response to a first antidepressant.

Methods: A Finnish cost-utility model with a 1-year time horizon (1) was adapted to a US setting and modified to include the burden of cognition. Published data were used for comparative efficacy (remission, relapse, and recovery), tolerability (withdrawal due to adverse events [AEs]), short- and long-term AE-related disutilities, and costs (direct and indirect). Health state-associated utilities were calculated using data from a randomized clinical trial of vortioxetine. Cognition-related inputs (residual cognition rates, disutilities, and cost) were derived from analyses of cognitive data (Digital Symbol Substitution Test and 5-item Perceived Deficits Questionnaire) reported in noninterventional (2) and randomized controlled trials (published articles and unpublished results). From the societal perspective, direct healthcare costs and indirect costs from absenteeism were considered. The main outcome was the incremental cost-effectiveness ratio (ICER).

Results: For vortioxetine, levomilnacipran, and vilazodone, the respective total costs (2015 US\$) were \$6615, \$6763, and \$6294; the respective initial treatment-line recovery rates were 34.1%, 28.3%, and 28.8%. Vortioxetine was associated with a greater quality-adjusted life-

year (QALY) of 0.0070 versus levomilnacipran, and of 0.0083 versus vilazodone. Thus, vortioxetine had lower costs and higher QALYs versus levomilnacipran (ie, dominant) and was cost-effective versus vilazodone (base case ICER, \$38,608/QALY). The residual cognition rates identified for vortioxetine, levomilnacipran, and vilazodone were 49.3%, 58.0%, and 63.7%, respectively. With inclusion of cognition-related inputs, vortioxetine was associated with a greater QALY of 0.0085 versus levomilnacipran, and of 0.0109 versus vilazodone. In the cognition scenario, vortioxetine also had lower costs and higher QALYs versus levomilnacipran (ie, dominant) and was cost-effective versus vilazodone (ICER, \$27,633/QALY). Inclusion of cognition burden reduced the ICER by 28% versus the base case. Similar results were found when considering direct costs only (more than 60% of total costs) in either scenario. The probability of being cost-effective was 80% at a \$50,000 willingness-to-pay threshold (recommended US-based lower limit).

**Conclusions:** In this analysis of MDD treatment after an antidepressant switch, vortioxetine showed higher QALYs and less cognitive impairment than levomilnacipran or vilazodone. It had lower costs versus levomilnacipran and was cost-effective versus vilazodone. Inclusion of the burden of cognition further increases the cost and QALY differentials in favor of vortioxetine. These findings suggest potential benefits of switching to vortioxetine.

#### **W44. EFFECT OF ADJUNCTIVE BREXPIRAZOLE ON METABOLIC PARAMETERS IN ELDERLY PATIENTS WITH MAJOR DEPRESSIVE DISORDER: ANALYSIS OF AN OPEN-LABEL, LONG-TERM, FLEXIBLE-DOSE STUDY**

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<sup>1</sup>Otsuka Pharmaceutical Development & Commercialization, Inc., <sup>2</sup>H. Lundbeck A/S,

**Abstract:** Background: Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and an antagonist at 5-HT<sub>2A</sub> and noradrenaline  $\alpha$ <sub>1B/2C</sub> receptors, all at similar potency [1]. Brexpiprazole is approved in the US for the treatment of schizophrenia and for use as adjunctive treatment in major depressive disorder (MDD) [2]. Here, we evaluate the long-term effect of adjunctive brexpiprazole on metabolic parameters in elderly patients with MDD based on data from an open-label, long-term study (Aquila; NCT02400346). The study also assessed efficacy by mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS).

**Methods:** Elderly patients ( $\geq 65$  years) with MDD, and inadequate response to  $\geq 1$  antidepressant treatment (ADT) received open-label, flexible-dose brexpiprazole (1-3mg/day) adjunctive to their current ADT for 26 weeks, including a 4-week titration period. Safety and tolerability assessments included adverse events (AEs), clinical safety laboratory tests, including change in total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, vital signs, and weight/body mass index.

**Results:** 132 patients were treated, and 88 (66.7%) completed the 26-week study. Main reasons for withdrawal were AEs (18.2%), and lack of efficacy (6.8%). The mean age was 71.4 years with 26.5% being  $\geq 75$  years; 81.1% were women. Mean baseline MADRS total score was 26.9. The mean modal dose of brexpiprazole was 1.9 mg/day. 102 patients (77.3%) had treatment-emergent AEs (TEAEs); TEAEs with the highest incidences were fatigue (15.2%), restlessness (12.9%) and increased appetite (9.8%) followed by akathisia, weight increased, anxiety and dizziness (each approximately 8%). The most common TEAE leading to withdrawal was

fatigue (3.0%). No clinically relevant patterns were seen in mean changes in clinical safety laboratory values, vital signs or weight. Two patients with potentially clinically significant metabolic parameter values had corresponding TEAEs. There were no new occurrences of diabetes mellitus. For fasting metabolic parameters, mean baseline values were: total cholesterol 206.98 mg/dL; HDL 63.81 mg/dL; LDL 117.10 mg/dL; triglycerides 132.16 mg/dL; and glucose 97.41 mg/dL. Mean changes from baseline to Week 26 (observed cases) were: total cholesterol -3.79 mg/dL; HDL -4.88 mg/dL; LDL 1.81 mg/dL; triglycerides -1.05 mg/dL; and glucose 4.05 mg/dL. Mean weight gain at week 26 was 0.9 kg and 12.3% of patients had a weight increase  $\geq 7\%$  at any time during the study. At Week 26, the mean change from baseline in MADRS was -14.5 (95% Confidence Interval: -16.2, -12.8).

Conclusion: Generally, adjunctive treatment with brexpiprazole was well-tolerated in elderly patients with MDD. Despite a modest mean weight increase, the mean changes in other metabolic parameters were small. Further, clinically meaningful improvements in depression severity were notable after up to 26-weeks of adjunctive treatment with brexpiprazole, suggesting that brexpiprazole may be useful as adjunctive treatment of MDD in the elderly.

#### **W45. INTERMITTENT EXPLOSIVE DISORDER: DSM-5 DIAGNOSIS PRIMED FOR A PHARMACOTHERAPEUTIC BREAKTHROUGH?**

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**Abstract:** The Diagnostic and Statistical Manual, Fifth Edition (DSM-5) defines Intermittent Explosive Disorder (IED) as the failure to control impulses, leading to behavioral outbursts of verbal or physical aggression. These outbursts are further characterized as being grossly out of proportion to the precipitating stressor and causing marked subjective distress or psychosocial impairment.

The prevalence of IED in the United States is estimated to be approximately 4%, indicating it is more widespread than other common psychiatric disorders. Usually beginning in late childhood or adolescence, IED can manifest as workplace violence, domestic abuse, or road rage - therefore presenting a potentially serious threat to public health. There are currently no FDA-approved treatments for IED, suggesting it is an unmet medical need.

IED is typically treated with cognitive behavioral therapy (CBT) and off-label pharmacotherapy from various classes (e.g., selective serotonin reuptake inhibitors, beta blockers, antipsychotics, lithium, and anticonvulsants). The evidence base supporting the efficacy and safety of these off-label treatments is variable and there is little regulatory evaluation of treatments.

Barriers to drug development for IED include an incomplete understanding of its natural history, the lack of a precedent pathway for pharmaceutical approval, fear of legal or adverse media attention if subjects commit violence, and the presence of confounding clinical conditions (e.g., substance use disorders, attention deficit hyperactivity disorder, and mood disorders). In this poster presentation, we will highlight the need for effective pharmacotherapy for IED as well as issues related to drug development for this indication from a regulatory perspective; these issues include clinical study design (e.g., outcome measures, subject eligibility criteria, duration, etc.) and drug approval pathways.

#### **W46. CONCOMITANT USE OF ATYPICAL ANTIPSYCHOTICS WITH LEADING PSYCHOTROPIC MEDICATION CLASSES AND THE RISK OF TYPE 2 DIABETES MELLITUS: A POPULATION-BASED STUDY OF MEDICAID INSURED YOUTH**

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**Abstract:** Background: More than half of Medicaid-insured youth treated with atypical antipsychotic (AAP) medications are also treated with concomitant antidepressants or stimulants, although the metabolic effects of such combinations are largely unknown. While there is no known biological/pharmacological plausibility for stimulant treatment-emergent risk of type 2 diabetes mellitus (T2DM), there is growing evidence—mostly in the adult literature—that antidepressants are independently associated with an increased risk of T2DM. Consequently, the primary objective of this study was to assess the risk of incident T2DM associated with concomitant use of antidepressant subclasses with AAPs in Medicaid-insured youth. We hypothesized that among AAP-treated youth, concomitant exposure to antidepressants would be associated with an increased risk of T2DM. Also, as a control, we assessed the risk for T2DM associated with the concomitant stimulant use with AAPs, hypothesizing that this combination would not be associated with an increased risk.

Method: Medicaid Analytic eXtract data were used to conduct a retrospective cohort study of youth (5-20 years) who initiated AAP treatment. In AAP-treated youth, concomitant antidepressant (serotonin reuptake inhibitors [SSRI/SNRIs], tricyclic/other cyclic antidepressants [TCAs], and other antidepressants) or stimulant use was assessed. Medication use was operationalized using three time-dependent measures: current/former/nonuse, duration of use, and cumulative dose exposure. The risk of incident T2DM was assessed using a previously validated algorithm (positive predictive value of 83.9%) and estimated using discrete time failure models, adjusting for disease risk score estimated using >125 baseline and time-dependent covariates.

Results: Among 73,224 AAP initiators, 43.0% had concomitant antidepressant use (76.4% were SSRI/SNRIs) and 43.8% had concomitant stimulant use. In current AAP-treated youth, concomitant SSRI/SNRI (relative risk [RR]=1.84, 95% CI=1.30-2.59) or TCA use (RR=2.75, 95% CI=1.28-5.87) was associated with an increased risk of T2DM. By contrast, concomitant use of other antidepressants or stimulants was not associated with an increased risk of T2DM. In concomitant users of AAPs and SSRI/SNRIs, the risk of T2DM increased with the duration of SSRI/SNRI use (RR=2.35, 95% CI=1.15-4.83 for ≥180 days vs. 1-180 days) as well as with the cumulative SSRI/SNRI dose (RR=1.99, 95% CI=1.08-3.67 for >2,700 mg vs. 1-2,700 mg fluoxetine dose equivalents)—after adjusting for the duration and cumulative dose of AAP use. By contrast, in concomitant users of AAPs and stimulants, neither duration nor cumulative dose of stimulants was associated with an increased risk of T2DM.

Discussion: In AAP-treated Medicaid-insured youth, concomitant SSRI/SNRI use was associated with a heightened risk of T2DM, which intensified with increasing duration and dose. In view of the growing complexity of atypical antipsychotic regimens in Medicaid-insured youth and low rates of baseline metabolic monitoring in youth initiating AAP treatment, the study findings suggest that complex AAP regimens should be used judiciously with appropriate cardiometabolic monitoring. Continued efforts are warranted to support



Medicaid oversight policies to assure safe, effective, and appropriate use of complex AAP regimens in youth populations.

**W47. HEALTHCARE PROFESSIONALS' SATISFACTION WITH A DIGITAL MEDICINE SYSTEM IN AN OPEN-LABEL STUDY OF ADULT PATIENTS TREATED WITH ORAL ARIPIRAZOLE**

*Ross Baker\*, Timothy Peters-Strickland, Cathy Zhao, Tao Wang, Margaretta Nyilas, Claudette Brewer, Erica Lawson, Ray Sanchez*

*Otsuka Pharmaceutical Development & Commercialization, Inc.*

**Abstract:** Background: The utility of a Digital Medicine System (DMS) that objectively measures and reports a patient's medication ingestion has been previously reported. The DMS comprises sensors (ingestible and adhesive patch) and software applications that provide objective medication adherence information to patients and healthcare professionals (HCPs).

Objective: To assess HCPs' satisfaction with the DMS based on survey questions

Methods: The study surveyed HCPs from 4 US study sites that enrolled adult patients with schizophrenia, bipolar 1 disorder, or major depressive disorder who were treated with oral aripiprazole. After a 1-week screening phase, patients who demonstrated  $\geq 50\%$  patch wear during a 2-week prospective phase were continued into a 6-week observational phase. HCPs answered 18 survey questions regarding the utility of the DMS at the end of the study (week 8). Responses to most of the questions were based on a 7-point Likert scale ranging from extremely difficult/strongly disagree (1) to neutral (4) to extremely easy/greatly agree (7). NCT02722967

Results: A total of 51 patients were screened, 49 were enrolled, 40 entered the observation phase, and 38/49 (77.6%) completed the study. The Physician Utility Survey was completed by study site HCPs (psychiatrists) for 48 of the 49 enrolled patients (1 enrolled patient was lost to follow-up). Among the survey responses, 81% indicated that the HCP dashboard was easy to use (Likert scale responses: 5=somewhat easy, 6=easy, or 7=extremely easy), 73% indicated that the DMS was helpful (somewhat helpful, helpful, or extremely helpful) to engage patients in self-management of their condition, and 67% indicated that the DMS was effective (somewhat effective, effective, or extremely effective) in decision-making for medication adherence. Most responses also suggested that the DMS was helpful (somewhat helpful, helpful, or extremely helpful) in improving quality of care (61%) and conversations with patients (69%) and added value to clinical care (somewhat agree, agree, or greatly agree; 71%). For most patients (75%), HCPs monitored the HCP dashboard during and between patient visits. Overall, HCPs ranked pill ingestion data, multiple dose notifications, patient-reported missed dose reason code, and missed dose notifications as the most important features on the HCP portal.

Conclusions: These results indicate that HCPs were satisfied with the DMS overall, and found the dashboard easy to use and the system functional for decision-making regarding medication adherence and engaging patients.

Disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

#### **W48. DO SUICIDALITY PHENOMENA FOLLOW A LINEAR OR A NON-LINEAR PROGRESSION OVER TIME?**

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**Abstract:** Objective: To investigate whether the progression of suicidality phenomena over time is linear or non-linear. The model of progressive, linear suicidality has been the basis of much research into risk and protective factors for suicidality. Understanding the progression of suicidality over time will help researchers build better predictive models of suicidality.

Design: Methods developed by Robert Stetson Shaw, a physicist at University of California at Santa Cruz to analyze data from an oscillator in 2- and 3-dimensional space (2D and 3D, respectively) were used. These methods are used in non-linear dynamics theory / non-linear systems theory / turbulence theory / deterministic chaos. We adapted his methodology to an analysis conducted on 3 databases collected from the same subject over time.

Results: The method used permitted the mathematical graphic modeling of suicidality phenomena over 3 years in the form of a 2D and 3D attractor. There was no linear relationship whatsoever between suicidal ideation and behavior over time. The results found a non-linear dynamic relationship of suicidality phenomena over time. There was no progressive, linear relationship of suicidality phenomena over time. There was no linear relationship whatsoever between the rate of change of relationship between suicidal ideation and behavior over time.

Conclusions: The relationship of suicidality phenomena over time is non-linear and dynamic. This data can be displayed graphically in the form of an attractor that reflects the underlying structure of suicidality and their dynamic change over time. To improve predictive models of suicidality, the progressive, linear models need to be abandoned in favor of non-linear, dynamic systems mathematical modeling that more accurately reflect the turbulence, the apparent unpredictability, and the dynamic nature of the complex system of suicidality as they move through time. This has major implications for the predictive modeling in theory and the prediction of suicidality in clinical practice.

#### **W49. ENHANCING SUBJECTS' AWARENESS OF KEY PLACEBO RESPONSE FACTORS: THE IMPORTANCE OF IMPLEMENTING A BRIEF EDUCATIONAL PLACEBO RESPONSE VIDEO**

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**Abstract:** Introduction: The placebo effect continues to plague Central Nervous System (CNS), addiction, and general medicine clinical trials (Enck et al., 2011) and be muting the potential pharmacological efficacy of new drugs. Weber et al. (2005) identified a plethora of factors that contribute to this effect, including site-subject interactions, subject expectations of benefit, lack of subject understanding of the placebo, and subject uncertainty of his/her role in the trial. The current study takes an important step in understanding how subjects can be educated about these key factors which ultimately may lead to reducing their response to the placebo.

**Methods:** This pilot study implemented a pretest-posttest randomized control group design. Subjects first signed the Informed Consent Form at the Screening Visit per their CNS, addiction, or general medicine placebo-controlled clinical trial. They then completed the Placebo Awareness Questionnaire (PAQ) containing 5 multiple choice questions (one correct answer per item) to assess subjects' awareness of the key factors related to the placebo response. Upon completion of the PAQ, subjects were randomly assigned to the control or intervention (video) group. Subjects in the intervention group immediately then watched a seven-minute educational video that addressed the factors identified by Weber et al. (2005). At the conclusion of the video, intervention participants completed the same PAQ without access to the first responses. To match the temporality of the experimental group, the control subjects completed the PAQ seven minutes after completing the first PAQ, and to ensure the video intervention and its potential lessons were not withheld from the control subjects they watched the video after completing the post-test PAQ.

**Results:** A comparison of the intervention and control groups by age/gender showed no statistical differences. After testing for normality, a repeated measures one-way analysis of variance (ANOVA) was calculated to assess between- and within-group differences of the intervention and control groups. The results indicated that there is a significant difference,  $F(2, 41) = 700, p < .001$ , between the intervention group and the controls, such that the intervention group was significantly better able to identify the factors (i.e., their role) associated with reducing a placebo response after watching the video as compared to the control group. Moreover, a Wilcoxon signed rank test indicated significant differences between the pretest and posttest intervention group ( $V=325, p<.001$ ) suggesting again that the intervention helped subjects learn the appropriate placebo response factors, whereas the control group showed no statistical difference between their pretest and posttest ( $V=77.50, p=.101$ ).

**Conclusions:** Despite having read and confirmed understanding by research site staff of the Informed Consent Form, subjects across the three different placebo-controlled study indications did not fully understand all of the key factors associated with the placebo response. However, the results indicated that subjects who watched a brief video addressing these factors had significantly greater awareness of the issues that affect the placebo response as compared to subjects who did not watch the video. Research sites and perhaps even rater training vendors are encouraged to implement such a program before subjects participate in their placebo-controlled trials. Further studies should be conducted for replicability purposes and suggestions for future studies are presented in the poster (e.g., does the current educational intervention actually influence placebo response in the clinical trial).

## **W50. A MODEL PSYCHOPHARMACOLOGY CURRICULUM FOR TEACHERS OF PSYCHIATRIC RESIDENTS**

*Ira Glick\**

*Stanford University School of Medicine*

**Abstract:** Started by the ACNP training committee in 1984, the ASCP Psychopharmacology Committee has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to psychiatric residents, medical students and primary care physicians. It has increasingly had global penetration. We present here the 9th edition of the Resident Curriculum, the 3rd edition for Medical Students and the 2nd edition for Primary Care. The ASCP Curriculum Committee composed of directors of both resident education as well as medical student education educators have developed materials related to the "what, why, and how" to teach and evaluate. In addition, for each curriculum, we included both a core series of lectures as well as optional lectures developed by experts in their fields. We have done follow-

ups on all three curriculums within the last 2 years. We describe here the process of revising, updating, and moving to a web-based curriculum. We present the content for the three curriculums. Based on the follow up of all three curricula, we have revised every lecture and updated the pedagogy. Depending on the size/resources of the program, teachers use the curriculum in its entirety or in parts. It works even in non-English speaking countries as committee members work with users to adapt/translate to local conditions and teaching strategies. It has been difficult to connect with primary care training programs. For residents, the curriculum is now in its 8th edition and has 88 lectures and over 4,000 slides. For teaching medical students and primary care physicians, there has never been a generally accepted curriculum or set of teaching materials specifically designed for them. There is a great deal to teach in the four-year curriculum and medical students have widely divergent career paths. This curriculum has 22 lectures. Having the curriculum web-based has improved availability although some programs globally still need a hard copy version.

## **W51. PIMAVANSERIN FOR THE TREATMENT OF PARKINSON'S DISEASE PSYCHOSIS: NUMBER NEEDED TO TREAT, NUMBER NEEDED TO HARM, AND LIKELIHOOD TO BE HELPED OR HARMED**

*Leslie Citrome<sup>\*1</sup>, James Norton<sup>2</sup>, Kathy Chi-Burris<sup>2</sup>, George Demos<sup>2</sup>*

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**Abstract:** Background: Pimavanserin is a highly selective serotonin 5-HT<sub>2A</sub> receptor antagonist/inverse agonist indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). The study aim is to review the evidence-base for PIM for the treatment of PDP using the metrics of evidence-based medicine, namely number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH), in order to better place this intervention into clinical perspective.

Methods: Efficacy outcomes of clinical interest include response with pimavanserin 34 mg/d (PIM), as taken from the pivotal 6-week registrational trial of PIM vs. placebo using 2 definitions of response: (a) Scale for the Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) total score decrease  $\geq 3$  points from baseline; (b) Clinical Global Impressions-Improvement scale (CGI-I) score of 1 (very much improved) or 2 (much improved). Also examined was remission as defined by reduction of 100% from baseline on the SAPS-PD. Tolerability outcomes of clinical interest, occurring at any time in available studies of PIM were assessed, including discontinuation because of an adverse event (AE). NNT and NNH, with respective 95% CIs, for PIM vs. placebo were calculated, as well as LHH. Results: At Week-6 responders, as defined by SAPS-PD point reduction  $\geq 3$ , were observed in 62/95 (65%) of subjects receiving PIM vs. 38/90 (42%) for placebo, for a NNT vs. placebo of 5 (95% CI 3-12). Using the CGI-I, responders were observed in 43/95 (45%) for PIM, vs. 22/90 (24%) for placebo, yielding a NNT vs. placebo of 5 (95% CI 3-14). Remission was observed in 13/95 (14%) of subjects receiving PIM vs. 1/90 (1%) for placebo, for a NNT vs. placebo of 8 (95% CI 5-19). For PIM as pooled from available studies, the most common AEs (as defined by a rate  $\geq 5\%$  and twice that for placebo) were peripheral edema as observed in 14/202 (7%) for PIM vs. 5/231 (2%) for placebo, for a NNH of 21 (95% CI 12-127), and confusional state, seen in 12/202 (6%) for PIM vs. 6/231 (3%) for placebo, for a NNH of 30 (not statistically significant). The discontinuation rate due to an AE was 16/202 (8%) for PIM vs. 10/231 (4%) for placebo, yielding a NNH of 28 (not statistically significant). LHH for response vs. an AE of peripheral edema, confusional state, or discontinuation because of an AE were 4.2, 6.0, and

5.6, respectively. LHH for remission vs. an AE of peripheral edema, confusional state, or discontinuation because of an AE were 2.6, 3.8, and 3.5, respectively.

Conclusions: In terms of LHH, PIM 34 mg/d is approximately 6 times more likely to result in clinical response rather than discontinuation due to an AE. Limitations: The data analyzed in this study are limited to dichotomous outcomes. The results may not be generalizable to patients outside the confines of a clinical trial.

## **W52. INDEPENDENT PREDICTORS OF HOSPITALIZATION IN FIRST EPISODE PSYCHOSIS: BASELINE RESULTS FROM THE NIMH-ETP STUDY**

*Jose Rubio\*, Nina Schooler, Delbert Robinson, Christoph Correll, John Kane*

*The Zucker Hillside Hospital*

**Abstract:** Background: Hospitalization is an undesirable event in the treatment course of psychotic disorders, as it is associated with restricted civil liberties, stigma, interruption of psychosocial and vocational adaptation, and increased healthcare costs. Unfortunately, hospitalization is a very common initial treatment contact for individuals with first episode psychosis (FEP). Despite its importance, the correlates of hospitalization in FEP are still insufficiently understood.

Objective: To identify variables that are independently associated with psychiatric hospitalization in FEP patients in a large sample of participants receiving care in non-academic settings in the US.

Methods: Altogether, 403 individuals (age=15–40 years), who met criteria for a psychotic spectrum disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, psychotic disorder NOS), had a maximum of one illness episode, and had been on antipsychotics for  $\leq 6$  months, were enrolled in the Recovery After an Initial Schizophrenia Episode-Early Treatment Program-ETP (RAISE-ETP) study. Patients were recruited at 34 nonacademic clinics in 21 states in the US. A comprehensive number of variables: sociodemographic characteristics; illness severity; comorbid conditions; clinical services utilization; and type of treatment upon enrollment were measured. Univariable analyses and multivariable logistic regression analyses were conducted to identify factors independently associated with having been hospitalized prior to enrollment in the RAISE-ETP study.

Results: Altogether, 316 FEP participants (78.4%) had been hospitalized prior to enrollment in RAISE-ETP. In the multivariable analysis, hospitalization was independently associated with predominant antipsychotic class/higher dose ( $p<0.01$ ), greater number of psychotropic medications ( $p<0.01$ ), longer duration in the immediate past treatment setting ( $p<0.01$ ), and shorter duration of untreated illness (DUP) ( $p<0.01$ ) (overall model:  $r^2=0.226$ ,  $p<0.0001$ ).

Discussion: Although no differences in illness severity were observed at the time of enrollment in the RAISE-ETP study, individuals with FEP and a history of psychiatric hospitalization seemed to have greater illness acuity, reflected by more aggressive antipsychotic regimens, higher number of psychotropic medications, having been treated for a shorter time in the most recent care setting, and a shorter time between onset of psychotic symptoms and initiation of treatment. The association between longer DUP and lack of hospitalization indicates that there is a subgroup of FEP individuals with a lower level of acuity, but not necessarily a lower level of illness severity, that go undiagnosed/untreated for long periods of time. The fact that the

identified variables were able to explain 22.6% of the variance indicates that other unmeasured factors play a role in the hospitalization of FEP patients that require further elucidation. Nevertheless, these results argue for the development of strategies that identify and treat individuals with FEP earlier, when the level of acuity does not yet reach the hospitalization threshold.

### **W53. PLASMA COTININE IS POSITIVELY CORRELATED WITH SCORES ON THE NIH TOOLBOX COGNITIVE MEASURES IN PATIENTS WITH SCHIZOPHRENIA**

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**Abstract:** Introduction and Objectives: Schizophrenia is associated with high prevalence of cigarette smoking and cognitive impairment. Furthermore, the relationship between cigarette smoking and cognition in patients with schizophrenia is inconclusive; improved cognition, worse cognition and no association have all been reported. Most of the previous studies have relied on patients' self-report in determining smoking status and amount smoked. The aim of this study is to evaluate the relationship between plasma cotinine (a metabolite of nicotine) and cognition in a sample of patients with schizophrenia.

Methods: 48 patients with schizophrenia (diagnosed with the Mini International Neuropsychiatric Interview version 5) were recruited during inpatient admission. Fasting plasma cotinine was determined by Liquid chromatography–mass spectrometry. Cognitive function was assessed with the NIH tool box cognitive battery (Picture vocabulary [PV], Flanker inhibitory control [FL], List sorting working memory [LS], Dimensional change card sort [DC], Pattern comparison process speed [PC], Picture sequence Memory [PS], and Oral reading recognition [OR]). Fluid Composite (FC), Crystallized Composite (CC) and Total Composite (TC) scores were also derived. We calculated Pearson correlations between the cognitive measures and plasma cotinine.

Results: Cotinine correlated positively with TC ( $r = 0.41$ ,  $p = 0.014$ ), CC ( $r = 0.35$ ,  $p = 0.037$ ), FL ( $r = 0.422$ ,  $p = 0.006$ ), DC ( $r = 0.44$ ,  $p = 0.004$ ), PC ( $r = 0.36$ ,  $p = 0.022$ ) and OR ( $r = 0.33$ ,  $p = 0.038$ ) respectively.

Conclusions: The results of this study are consistent with previous studies that have found a positive correlation between nicotine exposure and improved cognition in patients with schizophrenia. The findings of this study provide additional evidence to support the evaluation of brain nicotinic modulators for the treatment of cognitive impairment in schizophrenia.

### **W54. EFFICACY OF CARIPRAZINE IN PATIENTS WITH BIPOLAR MANIA BY BASELINE SYMPTOM SEVERITY**

*Lakshmi N. Yatham<sup>2</sup>, Willie Earley<sup>1</sup>, Cheng-Tao Chang<sup>1</sup>, Ágota Barabássy<sup>3</sup>, Irma Saliu<sup>\*1</sup>*

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**Abstract:** Background: Cariprazine, a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors, is FDA approved for the treatment of adults with schizophrenia or mixed/manic episodes associated with bipolar I disorder. The general efficacy and tolerability of cariprazine in patients with bipolar mania has been supported by 3 phase

II/III studies (NCT00488618, NCT01058096, NCT01058668). The objective of this post hoc analysis was to investigate how the baseline severity of manic symptoms influences the efficacy of cariprazine in adult patients with bipolar I disorder.

Methods: Data were pooled from the 3 similarly designed, 3-week, randomized, double-blind, placebo-controlled trials in adult patients with acute manic or mixed episodes associated with bipolar I disorder. Cariprazine was flexibly dosed (3-12 mg/day) in 2 studies; the third study used a fixed/flexible dose design (3-6 mg/day, 6-12 mg/day); all doses were combined for the pooled analysis. Patients were required to have a Young Mania Rating Scale (YMRS) total score  $\geq 20$  and Montgomery-Åsberg Depression Rating Scale total score  $\leq 18$  for inclusion in the studies. Data were stratified into tertiles using baseline YMRS total score cutoff thresholds to define the baseline severity of manic symptoms (YMRS  $\leq 29$ , YMRS  $>29$  and  $\leq 34$ , and YMRS  $>34$ ). Post hoc analyses evaluated least squares (LS) mean change from baseline to day 21 in YMRS total score using a mixed-effects model for repeated measures in subgroups categorized by baseline manic symptom severity.

Results: There were 350 patients in the  $\leq 29$  severity subgroup (placebo=160, cariprazine=190), 364 patients in  $>29$  and  $\leq 34$  subgroup (placebo=144, cariprazine=220), and 323 patients in the  $>34$  subgroup (placebo=125, cariprazine=198). In each subgroup, significantly greater LS mean change from baseline in YMRS total score was observed with cariprazine versus placebo at each visit ( $P < .05$  for each). At day 21, LS mean change from baseline was greater for cariprazine versus placebo in the  $\leq 29$  subgroup (-14.5 vs -9.7), in the  $>29$  subgroup (-17.0 vs -13.5), and in the  $>34$  subgroup (-23.3 vs -15.8). LS mean differences (95% CIs) at endpoint were significant for cariprazine versus placebo in all baseline symptom severity subgroups ( $\leq 29$ : -4.8 [-6.8, -2.8],  $P < .0001$ ;  $>29$  and  $\leq 34$ : -3.6 [-5.9, -1.2],  $P < .01$ ;  $>34$ : -7.5 [-10.4, -4.6],  $P < .0001$ ).

Conclusions: Results suggest that cariprazine was more effective than placebo in improving manic symptoms in patients with bipolar I disorder regardless of baseline mania symptom severity. For cariprazine, the difference versus placebo was largest in the subgroup with the most severe baseline symptoms.

## **W55. EFFICACY OF CARIPRAZINE IN SUBGROUPS OF BIPOLAR PATIENTS WITH MANIC EPISODES, MIXED EPISODES, AND WITH OR WITHOUT PSYCHOTIC SYMPTOMS**

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**Abstract:** Background: Cariprazine is a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. The general efficacy and tolerability of cariprazine in patients with bipolar mania has been supported by 3 phase II/III studies (NCT00488618, NCT01058096, NCT01058668). However, the efficacy of cariprazine in specific subpopulations of patients based on diagnostic features has not been assessed. This pooled analysis of the 3 phase II/III studies evaluated the efficacy of cariprazine versus placebo in patients with manic versus mixed episodes and in patients with and without psychotic symptoms.

Methods: Data were pooled from 3 similarly designed, 3-week, randomized, double-blind, placebo-controlled trials. Cariprazine was flexibly dosed (3-12 mg/day) in 2 studies; the third

study used a fixed/flexible dose design (3-6 mg/day, 6-12 mg/day); all doses were combined for the pooled analysis. Patients were required to have Young Mania Rating Scale (YMRS) total score  $\geq 20$  and Montgomery-Åsberg Depression Rating Scale (MADRS) total score  $\leq 18$  for inclusion in the studies. Using DSM-IV-TR criteria, patients were stratified into subgroups by manic or mixed episode and with or without psychotic symptoms. Efficacy assessments included change from baseline to week 3 in YMRS total score, YMRS response rates ( $\geq 50\%$  improvement), and YMRS remission rates (YMRS total score  $\leq 12$ ).

Results: Of the 1037 patients in the ITT population, 892 patients (86%) met criteria for manic episodes and 145 (14%) met criteria for mixed episodes; 282 patients (27%) presented with psychotic features. Cariprazine treatment was associated with significantly greater mean improvement in YMRS total versus placebo regardless of type of episode or presence of psychotic features. Least square mean differences (LSMD) for change in YMRS total score at week 3 were: manic=-5.7 ( $P<.0001$ ); mixed=-4.0 ( $P=.0254$ ); psychotic=-6.2 ( $P<.0001$ ); nonpsychotic=-5.0 ( $P<.0001$ ). A significantly greater proportion of cariprazine patients versus placebo patients met the criteria for response and remission in the manic (response: 58% vs 36% [ $P<.0001$ ]; remission: 45% vs 29% [ $P<.0001$ ]), psychotic (response: 53% vs 32% [ $P=.0005$ ]; remission: 43% vs 25%;  $P=.0017$ ), and nonpsychotic (response: 59% vs 38% [ $P<.0001$ ]; remission: 47% vs 31% [ $P<.0001$ ]) subgroups. Cariprazine versus placebo had numerically greater rates of response (cariprazine: 57%; placebo: 40%;  $P=.065$ ) and remission (cariprazine: 49%; placebo: 34%;  $P=.058$ ) in patients with mixed episodes; differences did not achieve statistical significance, probably due to small sample size.

Conclusions: In this pooled post hoc analysis, cariprazine was effective in reducing mania symptoms across multiple diagnostic subgroups, including patients with manic or mixed episodes and patients with and without psychotic features.

#### **W56. EFFICACY OF CARIPRAZINE ON NEGATIVE SYMPTOMS IN ACUTELY ILL PATIENTS WITH SCHIZOPHRENIA: A POOLED, POST HOC ANALYSIS**

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**Abstract:** Background: Primary negative symptoms measurably contribute to disease burden in patients with schizophrenia; antipsychotics have generally shown no efficacy on this domain. Cariprazine, a dopamine D3/D2 receptor partial agonist, is FDA approved for the treatment of adults with schizophrenia and mixed/manic episodes associated with bipolar I disorder. In a 26-week study in stable patients with predominant negative symptoms of schizophrenia, cariprazine was effective in the treatment of negative symptoms. We conducted a pooled post hoc investigation of cariprazine efficacy in a subset of patients with moderate to severe negative symptoms from 2 Phase II/III cariprazine trials to determine if the signal also existed in this acutely ill population.

Methods: Data were pooled from 2 randomized, double-blind, placebo- and active-controlled, fixed-dose studies of cariprazine in patients with acute exacerbation of schizophrenia. Analyses were conducted on a subset of patients who met the following criteria at baseline: Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS)  $\geq 24$ , PANSS



factor score for positive symptoms (PANSS-FSPS)  $\leq 19$ , and a score  $\geq 4$  on at least 2 of 3 PANSS items: blunted affect, passive/apathetic social withdrawal, and lack of spontaneity. Least squares (LS) mean changes from baseline to week 6 in PANSS-FSNS were estimated for placebo (PBO), cariprazine (CAR) 1.5-3 and 4.5-6 mg/d, risperidone (RISP) 4 mg/d, and aripiprazole (ARIP) 10 mg/d using a mixed-effects model for repeated measures. PANSS-FSNS response ( $\geq 20\%$  reduction from baseline) was also evaluated.

Results: A total of 317/1315 patients met the negative symptom criteria at baseline. The magnitude of LS mean change (SEM) from baseline in PANSS-FSNS was greater for CAR 1.5-3 mg/d (-6.3 [0.6]), CAR 4.5-6 mg/d (-7.8 [0.7]), RISP (-7.1 [1.0]) and ARIP (-5.3 [0.8]) than for PBO (-4.3 [0.6]). LS mean differences (LSMDs) versus PBO were significant for both CAR doses (LSMD [95% CI]: 1.5-3 mg/d=-2.0 [-3.6, -0.3],  $P=.0179$ ; 4.5-6 mg/d=-3.4 [-5.2, -1.7],  $P=.0002$ ) and RISP (-2.8 [-5.0, -0.5],  $P=.0149$ ), but not for ARIP (-1.0 [-3.0, 1.0],  $P=.3265$ ). The LSMD at week 6 was also significant in favor of CAR 4.5-6 mg/d versus ARIP (2.4 [4.5, -0.4],  $P=.0197$ ). The percentage of PANSS-FSNS responders was significantly higher with CAR treatment (1.5-3 mg/d: 54.3%, number needed to treat [NNT]=6; 4.5-6 mg/d: 69.7%, NNT=3) than with PBO (35.4%); response rates for RISP (52.9%, NNT=6) and ARIP (40.9%, NNT=19) were not significantly different from PBO.

Conclusion: In this subset of acutely exacerbated schizophrenia patients who had moderate to severe negative symptoms at baseline, CAR and RISP, but not ARIP, demonstrated significant improvements versus PBO on negative symptoms at week 6. Limitations include the short duration of negative symptom evaluation and the potential that improvements in at least some of the negative symptoms may have been secondary to improvements in positive symptoms.

#### **W57. LONG-TERM REMISSION WITH CARIPRAZINE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA: A POST-HOC ANALYSIS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, RELAPSE PREVENTION TRIAL**

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**Abstract:** Background: Long-term remission is an important treatment goal for patients with schizophrenia. Cariprazine, a dopamine D3/D2 receptor partial agonist antipsychotic, is FDA approved in the US for the treatment of adults with acute schizophrenia and mixed or manic episodes of bipolar I disorder. Post hoc analyses investigated the efficacy of cariprazine in maintaining remission in patients with stable schizophrenia symptoms.

Methods: Analyses used data from a long-term, randomized, double-blind, fixed-dose, placebo-controlled cariprazine relapse prevention study in patients with schizophrenia (NCT01412060). Patients were stabilized with cariprazine during a 20-week, open-label phase, and randomized 1:1 to cariprazine (3, 6, or 9 mg/d) or placebo for up to 72 weeks of double-blind treatment. Symptomatic remission was defined according to the Remission in Schizophrenia Working Group criteria (Andreasen et al, 2005): scores  $\leq 3$  (mild) on 8 Positive and Negative Syndrome Scale (PANSS) items: mannerisms and posturing, unusual thought content, blunted affect, social withdrawal, lack of spontaneity, delusions, conceptual disorganization, and hallucinatory behavior. Sustained remission was defined as meeting

remission criteria at the current visit and all prior double-blind visits; the percentage of patients with sustained remission for a duration of at least 6 months was also evaluated. Time to loss of sustained remission was estimated using Kaplan-Meier analysis. Hazard ratio estimate was based on a Cox proportional hazards regression model.

Results: At randomization, 169/200 (84.5%) patients met symptomatic remission criteria. During double-blind treatment, 60.5% of cariprazine- and 34.9% of placebo-treated patients sustained remission through the final visit (number needed to treat=4). Time to loss of sustained remission was significantly longer for cariprazine versus placebo ( $P=.0020$ ; hazard ratio [95% confidence interval (CI)]: 0.51 [0.33, 0.79]). Among all randomized patients, 39.6% of cariprazine- and 21.2% of placebo-treated patients had sustained remission at their final visit and for  $\geq 6$  months prior; odds ratio (95% CI) was significant in favor of cariprazine (2.44 [1.30, 4.55],  $P=.0057$ ). Significant differences favoring cariprazine were also observed for the proportion of cariprazine- (41.6%) versus placebo- (27.3%) treated patients with sustained remission for  $\geq 6$  consecutive months at any time during double-blind treatment (1.90 [1.05, 3.44],  $P=.0379$ ).

Conclusion: Cariprazine was associated with significantly higher rates and longer duration of sustained remission. The likelihood of sustaining remission for  $\geq 6$  consecutive months during double-blind treatment was generally greater for cariprazine versus placebo.

#### **W58. ALKS 3831 ATTENUATES DOSE-DEPENDENT, OLANZAPINE-INDUCED WEIGHT GAIN IN ADULTS WITH SCHIZOPHRENIA: ANALYSIS FROM A PHASE 2, RANDOMIZED, OLANZAPINE-CONTROLLED STUDY**

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**Abstract:** Background: While olanzapine (OLZ) is one of the most effective antipsychotics, the risk of severe weight gain is a major limitation. The current literature is conflicting as to whether oral OLZ-induced weight gain is dose dependent. A prior Phase 2 study was conducted to evaluate efficacy and safety of ALKS 3831, a combination of OLZ and samidorphan (SAM; a novel  $\mu$ -opioid receptor antagonist), in comparison to OLZ alone in adults with schizophrenia (SZ). Phase 3 studies are currently underway evaluating the efficacy and safety of ALKS 3831 using a fixed 10 mg dose of SAM. This post-hoc analysis of the Phase 2 study evaluates the dose dependent effects on weight gain for OLZ.

Methods: A Phase 2 study was conducted in subjects with stable SZ. All subjects ( $N=300$ ) were initiated on a flexible dose OLZ based on physician's judgment. After a 1 wk OLZ lead-in, subjects were randomized to receive one of 3 different treatments with ALKS 3831 (OLZ + 5, 10, or 20 mg SAM) or OLZ alone (OLZ + matched placebo) in a double-blind paradigm. Exploratory post-hoc analysis was conducted to determine whether there is a dose effect of OLZ on % change from baseline in mean body weight at the 12-week endpoint using mixed model with repeated measurements for those subjects receiving OLZ alone versus ALKS 3831 (OLZ + 10 mg SAM).

Results: The mean target OLZ dose was similar across all four treatment groups (11.5 mg/d; median 10.0 mg/d). Among subjects treated with OLZ alone, OLZ was associated with a greater amount of weight gain in a dose-dependent manner, with a mean % change in body weight at wk 12 of 3.3%, 4.1% and 4.8% for those with a mean daily OLZ dose of  $<10$  mg,

≥10-15 mg, and ≥15 mg respectively. In contrast, there was no dose-dependent effect of OLZ when given in the context of ALKS 3831 with a 2.6%, 2.6%, 0.4% change in body weight at wk 12 for OLZ dose of <10 mg, ≥10-15 mg, and ≥15 mg, respectively. ALKS 3831 was generally safe and well tolerated. The most common adverse events (≥5%) in all ALKS 3831 subjects relative to OLZ alone subjects were somnolence, sedation, and dizziness.

Conclusions: A dose-dependent effect of oral OLZ monotherapy on weight gain was observed in this study. This finding was no longer observed in the context of treatment with ALKS 3831 (ie, OLZ coadministered with 10 mg SAM). The data from this Phase 2 study suggest that the effects of ALKS 3831 on OLZ-induced weight gain occur across the full OLZ dose range.

#### **W59. CORRELATES OF DECREASED SYNAPTIC VESICLE GLYCOPROTEINS 2A (SV2A) IN SCHIZOPHRENIA: AN IN-VIVO [11C]UCB-J PET IMAGING STUDY**

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**Abstract:** Background: Converging lines of evidence from postmortem, neuroimaging and genetic studies suggest the presence of abnormalities in synaptic structure and function in schizophrenia (SCZ). The development of UCB-J, a novel Positron Emission Tomography (PET) ligand with high specificity for synaptic vesicle glycoproteins 2A (SV2A), offers a unique opportunity to image synaptic density in-vivo in the human brain.

The aim of the study was to measure synaptic density in SCZ using [11C]UCB-J and High Resolution Research Tomography (HRRT); and to relate synaptic density to disease phenomena, cognitive test performance and electrophysiological (EEG) correlates of memory. Methods: Chronic SCZ patients and healthy controls underwent PET imaging using [11C]UCB-J. [11C]UCB-J binding (VT) was compared between the two groups. EEG data were acquired while subjects participated in a modified verbal memory task. Cognitive assessment was performed using the CogState battery.

Results: Relative to age- and gender-matched controls, SCZ patients (n=6) showed global reductions (effect size,  $d = 0.87$ ) in [11C]UCB-J (VT) binding with greatest group differences in the amygdala. Theta activity during the encoding was highly correlated with [11C]UCB-J VT in DLPFC ( $p < 0.001$ ) and posterior cingulate ( $p = 0.042$ ). Regional synaptic density correlated with cognitive test performance on measures of attention and working memory.

Conclusions: These data show that synaptic density is decreased in SCZ. Synaptic density was found to correlate with task performance on cognitive tests and task-related theta-band power in brain regions relevant to encoding.

#### **W60. VARIABLE FREE FATTY ACID COMPOSITION ASSOCIATED WITH SREBF IN SCHIZOPHRENIA PARTICIPANTS TAKING ATYPICAL ANTIPSYCHOTICS**

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**Abstract:** Background: Abnormal lipid homeostasis may play an important role in mediating the risk for metabolic disorders in schizophrenia. The sterol regulatory element-binding transcription factor (SREBF) genes regulate cholesterol and fatty acid synthesis. Among SREBF isoforms, both SREBF1 and SREBF2 have been shown to be upregulated by atypical antipsychotics (AAPs), but SREBF1 is more active in regulating fatty acid synthesis. This is particularly important in schizophrenia as AAPs are widely prescribed as maintenance therapy. In a preliminary analysis, we examined associations between a SREBF1 (rs11868035) variant, and free fatty acid (FFA) composition in a cohort of schizophrenia participants taking AAPs. Methods: All participants were from a cross-sectional study on cardiovascular disease risk in schizophrenia that involved fasting blood collection. Inclusion criteria for this pilot analysis included AAP use, and the absence of type two diabetes or use of anti-diabetic medication. AAP exposure was normalized using chlorpromazine equivalents. Fasting FFAs were quantified by gas chromatography after extraction from serum, and pyrosequencing identified SREBF1 (rs11868035) alleles. Regression modeling was used to predict FFA composition with the following variables: SREBF1 A allele carrier status, fasting insulin (a known regulator of SREBF gene expression), AAP exposure, BMI, and the interaction between A allele carrier status and AAP exposure.

Results: Eighty-one participants were included (mean age =  $45.7 \pm 7.8$  years) and 50.1 % carried the A allele. Mean fasting insulin was  $21.1 \mu\text{U/mL}$  ( $\pm 14.7 \mu\text{U/mL}$ ), 42.0 % were female, average BMI was  $32.0 \text{ kg/m}^2$  ( $\pm 8.0 \text{ kg/m}^2$ ), and average AAP exposure was 609 mg ( $\pm 385$  mg). The A allele carriers trended towards a lower average BMI ( $p=0.05$ ). Thirty-six long chain fatty acids were quantified for each participant. Regression analysis resulted in models that significantly predicted FFA composition for 6 fatty acids (18:2, 16:1, 16:0, 18:1 (n-9), 14:0, and 20:3) ( $p<0.05$ ). SREBF carrier status was a significant fixed effect in models for 16:1 and 20:3 ( $p=0.04$ ) where the A allele was associated with decreased FFA concentration for 16:1, and increased concentration for 20:3. An interaction between AAP dose and the A allele showed that AAP exposure was associated with 16:1 concentration ( $p=0.03$ ). Finally, fasting insulin was inversely correlated to 18:2 ( $p=0.003$ ), and positively correlated to 16:0 ( $p=0.006$ ) and 14:0 ( $p=0.0073$ ) concentrations.

Conclusion: To the best of our knowledge this is the first study investigating the interaction between SREBF1 rs11868035, AAP exposure, fasting insulin, and FFA composition in schizophrenia. An interesting relationship identified in this study is the association between the SREBF1 variant and 16:1. Previous research has identified increasing concentrations of 16:1 with adiposity, and the SREBF1 A allele with insulin resistance and adverse lipid labs. However, in our study BMI was not significantly associated with 16:1 composition, and presence of the SREBF1 A allele was only associated with increased 16:1 composition in the setting of higher AAP exposure. Future research will need to determine the extent to which the fixed effects studied in these models impact FFA composition when compared to healthy control subjects with and without schizophrenia. This will improve understanding of the relationship between lipid changes as they relate to AAP exposure or the underlying schizophrenia disease; ultimately determining the clinical impact of these variables and if a precision medicine dosing approach is beneficial in this setting.

## **W61. EVALUATION OF THE POTENTIAL FOR CONCOMITANT MEDICATIONS TO AFFECT VALBENAZINE PHARMACOKINETICS**

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**Abstract:** Background: Valbenazine (VBZ) is a vesicular monoamine transporter 2 (VMAT2) inhibitor in development for the treatment of tardive dyskinesia (TD). The potential for concomitant medications to affect VBZ pharmacokinetics (PK) was assessed through in vitro and clinical studies.

Methods: In vitro studies identified cytochrome P450 (CYP) and other enzyme systems responsible for metabolism of VBZ and its active metabolite, NBI-98782, and assessed the potential for VBZ and NBI-98782 to be P-glycoprotein (P-gp) transporter substrates. The potential for concomitant ketoconazole (KETO, strong CYP3A4 inhibitor) and rifampin (RIF, strong CYP3A4 inducer) to affect VBZ PK was evaluated in single-center open-label studies in healthy subjects. In one study, 24 healthy male (N= 12) and female (N=12) subjects received a single VBZ 50 mg dose prior to (Reference) and during (Test) a 5-day regimen of 200 mg KETO twice-daily. In the second study, 12 healthy male (N=6) and female (N=6) subjects received a single VBZ 80 mg dose prior to (Reference) and during (Test) a 10-day regimen of 600 mg RIF once-daily (QD). VBZ and NBI-98782 plasma concentrations were determined for 96 hours post-VBZ dosing. PK parameters were determined using standard non-compartmental methods. Statistical analyses were conducted by determining the point estimate and two-sided 90% confidence interval (CI) for Test to Reference (T/R) differences of log-normalized PK parameters. In a Phase 3 study, patients with TD on stable concomitant medications were administered 40 or 80 mg VBZ QD. Mean dose-normalized VBZ and NBI-98782 plasma concentrations at Weeks 2, 4, and 6 in patients receiving concomitant CYP2D6 inhibitors were compared to respective concentrations in subjects not receiving a CYP2D6 inhibitor.

Results: In vitro studies indicated that VBZ was primarily metabolized to NBI-98782 by non-CYP hydrolysis and to oxidative metabolites by CYP3A4. NBI-98782 was primarily metabolized by CYP2D6 and CYP3A4. Neither VBZ nor NBI-98782 were determined to be P-gp substrates. Plasma VBZ and NBI-98782 concentrations were higher with concomitant KETO and lower with concomitant RIF. In the KETO study, T/R ratios of VBZ and NBI-98782 C<sub>max</sub> were 151% (90%CI: 141-162%) and 163% (90%CI: 154-173%), respectively. T/R ratios of VBZ and NBI-98782 AUC<sub>inf</sub> were 214% (90%CI: 204-224%) and 207% (90%CI: 198-215%), respectively. In the RIF study, T/R ratios of VBZ and NBI-98782 C<sub>max</sub> were 68.2% (90%CI: 57.9-80.3%) and 48.5% (90%CI: 41.3-56.9%), respectively. T/R ratios of VBZ and NBI-98782 AUC<sub>inf</sub> were 27.7% (90%CI: 25.5-30.1%) and 22.8% (90%CI: 20.5-25.4%), respectively. In the Phase 3 study, mean (±SD) dose-normalized VBZ concentrations were similar with (3.38±2.36 ng/mL/mg) or without (3.68±2.04 ng/mL/mg) concomitant CYP2D6 inhibitors. Dose-normalized NBI-98782 concentrations were also similar with (0.534±0.321 ng/mL/mg) or without (0.513±0.326 ng/mL/mg) concomitant CYP2D6 inhibitors.

Conclusions: In vitro and in vivo data consistently demonstrated that CYP3A4 metabolism is an important elimination pathway for VBZ and NBI-98782. Specific guidelines for administering VBZ concomitantly with potent CYP3A4 inducers and inhibitors will assist management of VBZ treatment in clinical practice. Although CYP2D6 metabolism contributed to elimination of NBI-98782, a clinically-relevant effect of potent CYP2D6 inhibitors on NBI-98782 PK was not apparent.

## **W62. NEUROCOGNITION AND DURATION OF UNTREATED PSYCHOSIS IN FIRST EPISODE PSYCHOSIS: FINDINGS FROM THE RAISE-ETP STUDY**

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**Abstract:** Introduction: There is increasing evidence that cognitive impairment is a core feature of schizophrenia. Furthermore, it has been observed that executive dysfunction is present prior to the first episode of psychosis. The relationship between duration of untreated psychosis (DUP) and cognitive functioning in patients with first episode psychosis (FEP) is uncertain. Some studies have found a significant relationship between shorter DUP and better overall cognitive function, others failed to find such a relationship. These differences may be in part attributable to numerous factors such as sample size, study design and neuropsychological tests used. Recovery After an Initial Schizophrenia Episode- Early Treatment Program (RAISE-ETP) was designed to compare a team based integrated treatment program (Navigate) to usual care (Community Care) in patients with FEP. The study was conducted at community treatment settings in the US. We examined the relationship between DUP and cognitive measures at study entry and address the following question: Is longer DUP associated with poorer scores in the Brief Assessment of Cognitions in Schizophrenia (BACS)?

Methods: There were a total of 404 subjects (223 in the Navigate arm and 181 in the Community Care arm) at 34 sites across the US. The mean age in Navigate was 23.5 years; it was 23.2 in Community Care. Diagnoses were confirmed using SCID-IV and included schizophrenia, schizoaffective disorder, schizophreniform disorder or psychosis NOS. Subjects were not exposed to more than 6 months of antipsychotic medications. Cognitive testing was performed using the BACS at baseline and at 1 and 2 years. The measures included list learning (verbal memory), digit sequencing (working memory), token motor task (motor speed), semantic and letter fluency (verbal fluency), symbol coding (attention and processing speed), tower of London test (executive functioning) yielding a composite score. We used Spearman's rank correlation to examine the effects of DUP on each of the seven cognitive measures. As the DUP was not normally distributed, we used log DUP in the analyses.

Results: The median DUP for the entire sample (403 subjects) was 74 weeks. The distribution was bimodal. At study entry, the composite score for cognitive testing (t-score) was 29.4 for Navigate and 28.9 for Community Care. There was no significant relationship between DUP and any of the six cognitive domains or the composite score.

Discussion: The lack of relationship between DUP and cognitive functioning in this sample would be consistent with the view that the onset of psychosis does not have an additional effect on cognition beyond a pre-psychotic state. This would be contrary to the "neurotoxic hypothesis" that proposes that psychosis might have a toxic effect on the brain. Further analyses will be presented to examine the relationship of moderator variables to DUP.

## **W63. A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 6-WEEK STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TAK-063 IN SUBJECTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA**

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**Abstract:** Current treatments for schizophrenia generally have significant side effects and show limited efficacy across symptom domains. TAK-063 is a novel, potent, and selective inhibitor of phosphodiesterase 10A, an intracellular enzyme selectively expressed in the medium spiny neurons of the striatum. TAK-063 has shown efficacy in animal models of schizophrenia, and was shown to be safe and well tolerated in phase 1 studies of healthy subjects and subjects with stable schizophrenia. This study evaluated the efficacy and safety of 20-mg daily TAK-063 versus placebo in subjects with acutely exacerbated symptoms of schizophrenia. Adults aged 18 to 65 with diagnosed schizophrenia and psychotic symptoms that had exacerbated within 60 days of screening were randomized 1:1 to 6 weeks of placebo or TAK-063 taken once daily at night with food. Dose down-titration was allowed (blinded) to TAK-063 10 mg for intolerability. Subjects were hospitalized for the first 3 weeks and could be discharged afterwards at investigator's discretion. The primary endpoint was the least-squares (LS) mean change from baseline in total PANSS score at week 6. The study was powered (80%) to detect a difference on the total PANSS of 10 points at week 6, with a common standard deviation of 20 points (standardized effect size=0.5). Secondary endpoints included the LS mean changes in Clinical Global Impression-Severity (CGI-S) scale, Clinical Global Impression-Improvement (CGI-I) scale, and PANSS Marder Factor scores at week 6. Of the 164 subjects enrolled (n=81, placebo; n=83, TAK-063), 106 completed the study. With the exception of race, the treatment groups were similar; 43 and 65 black subjects were enrolled in the placebo and TAK-063 groups, respectively. The LS mean change from baseline in total PANSS score at week 6 was approximately -14.1 points in the placebo group and approximately -19.5 points in the TAK-063 group (LS mean difference=-5.46; standard error=3.44; p=.115, effect size=0.308) from the mixed model repeated measures analysis. Secondary endpoints were generally supportive of antipsychotic efficacy. The effects on PANSS positive, negative, and general psychopathology subscales and Marder Factors were generally consistent with the changes in Total PANSS. The change from baseline CGI-S at week 6 was -0.76 points in the placebo group and -1.19 points in the TAK-063 group (LS mean difference=-0.43, standard error=0.202, p=.035, effect size=0.413). Changes in CGI-I score favored TAK-063 (LS mean difference=-0.66, standard error=0.244, p=.007, effect size=0.530). Consistent with phase 1 findings, TAK-063 was safe and well tolerated. The rates of all-cause discontinuation were similar between groups. The number of down-titrations was equivalent in each group (1 each). The most frequent treatment-emergent adverse event (TEAE) was somnolence (2.5% placebo vs. 12.0% TAK-063). Extrapyramidal syndromes (EPS) were reported in 12.3% of subjects in the placebo group and 27.7% in the TAK-063 group. There was no difference from placebo in Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) score. TEAEs of EPS graded as "severe" were reported in 2 subjects receiving 20-mg TAK-063.

While the study did not meet its primary endpoint, the data are generally supportive of potential efficacy in the treatment of schizophrenia. Interpretation of the results is confounded by the lack of dose-ranging and active treatment reference.

#### **W64. MEASURING THE ELEMENTS OF DESIRE IN THE BREMELANOTIDE RECONNECT STUDY**

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**Abstract:** Objectives: To evaluate the measurement properties of the Elements of Desire Questionnaire (EDQ) using pooled data from the RECONNECT study of bremelanotide (BMT) in the treatment for in premenopausal women.

Materials/Method: The RECONNECT study comprises 2 Phase 3, multicenter trials consisting of a 4-week screening period; a Core Phase (4-week at-home placebo period to establish baseline followed by a 24-week randomized, double-blind treatment period); and an ongoing 52 open-label extension. Participants self-administered BMT (1.75 mg) or placebo subcutaneously using an auto-injector, as-desired, prior to sexual activity. The co-primary-endpoints were change in the desire domain of the Female Sexual Function Index (FSFI-D) and the Desire score on the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO). The FSFI-D is a 2 item desire scale and the FSDS-DAO desire score is a single item; both were completed at every clinic visit. The EDQ is a more comprehensive assessment of desire (9 items) and was used to explore changes in the experience of desire over the course of the trial. Participants completed the EDQ daily version for 7 consecutive days prior to Visits 2, 3, 6, and 9 and the EDQ monthly version at every clinic visit. The analysis population consisted of all subjects with FSFI data at baseline and  $\geq 1$  follow-up visit. Cronbach's  $\alpha$  was used to measure the internal consistency of participants' responses to the EDQ. Test-retest reliability was evaluated using the intraclass correlation coefficient (ICC). Correlations between the EDQ and other measure of FSD were quantified using Spearman's correlation coefficient.

Results: Both studies met the pre-specified co-primary efficacy endpoints. 1267 participants were randomized and 1198 participants were included in the evaluable population. The EDQ (monthly and daily versions) demonstrated good internal consistency, test-retest reliability, and construct validity. Cronbach's  $\alpha$  ranged from 0.86 (visit 2) to 0.96 (visit 9) for the monthly recall and from 0.91 to 0.97 for the 24-hour recall. There was no evidence of a ceiling effect in either the monthly or 24-hour recall versions on the EDQ at any time point. The monthly recall and 24-hour EDQ scores were highly correlated: Spearman's coefficients  $r_s \geq 0.76$ ; and ICCs 0.64 (visit 3) to 0.83 (visit 9). There was a higher rate of missing data for the 24-hour recall (40% to 54% fewer participants) compared with the monthly recall version. Moderate to large correlations were observed between the monthly EDQ scores and other desire-related scales; FSFI desire domain ( $r_s=0.79$  and  $0.87$ , visits 3 and 6, respectively), FSDS-DAO item 13 ( $r_s=0.51$  and  $0.60$ ), FSEP-R desire item ( $r_s=0.60$  and  $0.64$ ); FSDS-DAO total score ( $r_s=0.54$  and  $0.61$ ), FSFI total score ( $r_s=0.63$  and  $0.75$ ), General Assessment Questionnaire: Item 3 ( $r_s=0.51$  and  $0.66$ ); as well as the WITS-9 total score ( $r_s=0.65$  and  $0.76$ ).

Conclusions: The EDQ may provide additional insight about the effects of treatment on the experience of women's desire and interest. Given the high rate of non-compliance for the daily version the monthly recall version of the EDQ may be a better option for clinical trials.



**W65. THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS: EFFECTS OF FETAL EXPOSURE ON RISK FOR MAJOR MALFORMATIONS**

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**Abstract:** Background: Despite widespread use of atypical antipsychotics in women of childbearing potential, reproductive safety data across these medicines are sparse. The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) at Massachusetts General Hospital was established in 2008 to address this knowledge gap. Website: [www.womensmentalhealth.org/pregnancyregistry](http://www.womensmentalhealth.org/pregnancyregistry). Toll-free number: 1-866-961-2388

Methods: Data are prospectively collected from pregnant women, ages 18-45 years, using 3 phone interviews conducted at the time of enrollment, 7 months gestation, and 3 months postpartum. The exposed group is comprised of women who have taken one or more atypical antipsychotics during pregnancy; the comparison group is comprised of women who have not taken this class of medication during pregnancy. Information regarding the presence of major malformations is abstracted from the medical records along with other data regarding maternal and neonatal health outcomes. Identified cases of major malformations are sent to a dysmorphologist blinded to drug exposure for adjudication. A scientific advisory board, consisting of experts in the fields of teratology, pharmacoepidemiology, and psychiatry, governs the release of findings.

Results: As of January 11, 2017, total enrollment in the Registry was 856 women: 539 women in the exposed group and 317 women in the comparison group. A total of 489 women have completed the study and were eligible for inclusion in the analysis. The proportion of study subjects for whom medical records were obtained was 82%. Of 312 live births with first trimester exposure to atypical antipsychotics as a class of medications, four major malformations were confirmed. Of 138 live births with first trimester exposure to quetiapine, one major malformation was confirmed. Of 96 live births with first trimester exposure to aripiprazole, three major malformations were confirmed. Of the 177 comparison group live births, one major malformation was confirmed. The absolute risk of major malformations was 1.3% among infants exposed to an atypical antipsychotic during the first trimester and 0.6% among unexposed infants. The risk ratio for major malformations was 2.27 (95% CI: 0.26-20.15) comparing exposed to unexposed infants, not reaching statistical significance.

Discussion: The NPRAA offers a systematic way to collect prospective reproductive safety information which informs the care of women who may use atypical antipsychotics to sustain psychiatric well-being. This preliminary analysis indicates that these agents are not major teratogens but further information is needed to better estimate risk. The importance of pregnancy registries is underscored by recent FDA guidance (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>).

## **W66. ASSESSING THE ADEQUACY OF THE BLIND: AN ANALYSIS OF DATA IN IV KETAMINE FOR RAPID TREATMENT OF DEPRESSION STUDY**

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*Baylor College of Medicine*

**Abstract:** Background: Intravenous Ketamine for rapid treatment of depression is an expanding field of research with promising results to date. However, despite many trials demonstrating rapid and significant efficacy of IV Ketamine for treatment resistant depression, the validity of these findings may be questioned because of uncertain blinding quality. control condition. A recent parallel-arm randomized controlled trial in 73 patients with TRD by Murrough et al 2013 attempted to address limitations of this design by comparing a single infusion of ketamine (0.5 mg/kg) to midazolam (0.045 mg/kg) infused over 40 minutes in which they found that the likelihood of response at 24 hours as measured by MADRS score was greater with ketamine than with midazolam (odds ratio, 2.18; 95% CI, 1.21 to 4.14), with response rates of 64% and 28%, respectively. These findings, however, are potentially limited by continued uncertainty about the integrity of masking procedures.

Methods: The present analysis is two-pronged. First, we assessed the adequacy of the blind by analyzing guess data. Next, we assessed whether deficiencies in the integrity of the blind resulted in bias. We compared those who remained blinded versus those who became unblinded in both placebo and treatment arms with respect to CADSS score at 40 min, whether the anesthesiologist intervened, the response (defined as 50% reduction in MADRS), remission (defined as MADRS  $\leq$  9), relapse (defined as a MADRS  $>15$  at 7 days), and baseline expectancy. Additionally, we examined expectancy and how this measure related to unblinding and outcome as a reflection of a source of potential bias.

Results: Of those patients who received midazolam and among those who received ketamine, there was no significant difference in any of the above measures between blinded and unblinded patients at 40 minutes or at 24 hours (except for more anesthesiologist intervention in those who correctly guessed at 24 hours that they had received ketamine ( $p=0.04$ ). When a rater incorrectly guessed that a patient had received active treatment, they were more likely to measure a response in these patients ( $p=0.02$ ). In the ketamine group, those who were rated by persons who correctly guessed that they had received ketamine had higher response rates ( $p=0.01$ ) as well as higher remission ( $p=0.0001$ ). Those who were more optimistic in their thinking and feeling (as measured with baseline expectancy) in the midazolam group were more likely to respond (Fisher's  $p=0.03$  in "think" and  $p=0.01$  in "feel"). The higher the baseline expectancy the more negative or greater the reduction in MADRS score or response.

Conclusion: We found that the blind was enhanced but imperfect, and unblinding did not result in any statistically significant bias in outcome. Expectancy only impacted response outcome in the placebo group. In general, and with ketamine trials in particular, it is necessary to assess the adequacy of the blind. We demonstrated a potential means to assess said blind as well as the impact of unblinding on results. Our data analysis gives a scientific illustration and statistical credence to the potency of the placebo effect. We suggest that all studies, especially those with an identifiable treatment drug and those with a potentially subjective outcome measure, include an assessment of the adequacy of the blind in the data analysis.

## **W67. BODY TEMPERATURE RISES FOLLOWING SUCCESSFUL ECT TREATMENT OF DEPRESSION: DOES BODY TEMPERATURE DECLINE**

## **DURING DEPRESSION DUE TO DYSFUNCTIONAL THERMOREGULATORY PATHWAYS?**

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*Saint Louis University School of Medicine*

**Abstract:** Background: Depression has been hypothesized to be associated with dysfunctional thermoregulatory pathways. Patients with depression have been shown to have higher body temperatures and decreased ability to regulate their body temperature. Recent studies demonstrated possible efficacy in treating depression using heat. Given that spontaneous, non-infection related, generalized seizures transiently increase body temperature, we wanted to investigate the potential correlation between electroconvulsive therapy (ECT) and thermoregulatory mechanisms in depression.

Methods: A retrospective chart analysis was conducted where electronic health records (EHR) of subjects diagnosed with depression (unipolar or bipolar) and treated with a full course of ECT were reviewed. 33 Subjects met the criteria for inclusion (Mean age  $61 \pm 18$ , 20 male and 13 female). All subjects were treated inpatient for recurrent, severe symptoms and were all naïve to ECT treatment prior. Each subject received multiple ECT sessions ( $9.7 \pm 2.9$ ) until remission of symptoms, up to a full course of ECT. 27 of the depression group were diagnosed with major depressive disorder (MDD) and 6 were diagnosed with bipolar disorder (BPD). Oral temperature recordings pre- and post-ECT for the first ECT and the last ECT were collected for each subject. Statistical analysis was performed using paired t-test.

Results: No significant change in mean body temperature occurred after the initial ECT treatment ( $p=0.33$ , mean body temperature change  $+0.094 \pm 0.55^\circ\text{F}$ ), but a significant increase was found between the mean baseline body temperature and mean body temperature after the final ECT treatment when the depression had improved ( $p=0.009$ , mean body temperature change  $+0.218 \pm 0.45^\circ\text{F}$ ). All depression subjects achieved remission of symptoms by the end of the ECT course and were deemed ready for discharge.

Conclusion: Our data suggest that improvement in clinical depression appears to be associated with an increase in body temperature. It may also imply that body temperature drops during an episode of depression and returns to normal [i.e. increases] following effective antidepressant treatment like ECT. It is noteworthy that the baseline temperature was not significantly elevated following the first ECT-induced seizure, when efficacy has not yet occurred, but it did increase significantly after the full course of about 10 ECT treatments had been administered, with remission of the depressive symptoms. Efficacy appeared to be associated with restoration of thermoregulatory mechanisms that could be disrupted during depression. Replication of these findings with larger samples is warranted.

## **W68. USING AN ARTIFICIAL INTELLIGENCE PLATFORM ON MOBILE DEVICES TO MONITOR AND INCREASE ADHERENCE IN SUBJECTS WITH SCHIZOPHRENIA**

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**Abstract:** Objective: The need to ensure optimal adherence is critical in Phase 1 clinical trials, particularly in ambulatory subjects. An artificial intelligence (AI) platform was evaluated as a real-time monitoring method for study drug adherence and to examine the feasibility of using the platform as a tool to increase adherence and retention in a Phase 1b, randomized, double-blind, cross-over study in patients with negative symptoms of schizophrenia treated with antipsychotics.

Design: Subjects in the ongoing BP29904 study are randomized to one of six treatment sequences, during which each patient received three 3-week treatment courses. Treatment periods are separated by a washout of 14 days. Subjects are given smartphones with the AI application downloaded and asked to use the AI application once daily for the administration of two capsules. The primary adherence measure for the study is based on AI platform adherence data.

Results: The AI platform has been used by 29 subjects so far, totaling 1,131 subject days; 2,262 adherence parameters have collected. In the current patient sample the mean (SD) age is 37.0 (6.6) years and 92.6% of the subjects are male; 66.7% of subjects are black, 25.9% white, and 7.4% Asian. For randomized subjects who have received at least 1 dose of the study drug, mean (SD) cumulative dose adherence measured by the AI platform (visual confirmation of drug ingestion) and scheduled pill counts was 95.0% and 99.7%, respectively.

Conclusion: Subjects with negative symptoms of schizophrenia treated with antipsychotics in an ongoing 15-week Phase 1b cross-over study demonstrate high rates of adherence using a mobile AI application. Estimated non-adherence in previous CNS trials based on PK data ranges from 13% to 39% (1) with a dropout rate frequently over 30% (2). Use of the platform has reduced non-adherence to 5% in this ongoing study. This study demonstrates the feasibility of using AI platforms to ensure high adherence and acceptability by patients, provide reliable adherence data, and rapidly detect non-adherence in CNS trials. In the presentation, the final adherence data of this study will be presented.

## **W69. A PILOT STUDY OF ACUTE ANTI-PSYCHOTIC-INDUCED BLOOD PRESSURE CHANGES AMONG PSYCHIATRIC INPATIENTS**

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**Abstract:** Background: Long-term and chronic cardiovascular and metabolic effects of antipsychotic medications are well known and cannot be overemphasized; however, the acute effects are not well known.

Method: A one-year retrospective chart review of 60 randomly selected adult psychiatry inpatients that comprised 20 patients from each of the categories of DSM-IV-TR diagnoses including schizophrenia, schizoaffective disorder and bipolar. Data was collected for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes of  $\geq 20$  mmHg within the 24 hours following administration of any antipsychotic medications. Data was analyzed in SAS version 9.3 [SAS, 2012] using Pearson correlation and Analysis of Variance (ANOVA) to test association between acute blood pressure ( $\geq 20$  mmHg change in SBP and DBP: yes versus no) and antipsychotic administration within 24 hours.

Results: Blood pressure decrease in both SBP and DBP was the most common acute change. However, only olanzapine, fluphenazine and ziprasidone showed significant correlations with reduction in SBP and DBP. In ANOVA regressions, the associations with BP changes were significant only for SBP.

Conclusion: The results suggest that antipsychotic administration may be acutely associated reduction in BP within 24 hours of administrations of medication. Further well designed prospective studies are needed to replicate these findings.

**W70. ARE THERE CULTURAL DIFFERENCES IN DEPRESSION SYMPTOM EXPRESSION AS MEASURED BY THE HAMD-17 IN PATIENT COHORTS IN NORTH AMERICA AND EASTERN EUROPE/RUSSIA?**

*William Yavorsky\*, Kristy Wolanski, Nina Engelhardt, Cynthia McNamara, Francisco Burger, Guillermo DiClemente*

*Cronos CCS*

**Abstract:** Introduction: Clinical trials in depression often use the same instrument to measure symptom expression whether it is the MADRS, the HAMD or some other standardized endpoint. Some have questioned whether these instruments hold up across patient and indeed rater cohorts where symptom expression and training may differ from the social and clinical context in which the instruments were developed (e.g., Targum, 2013). In this study we sought to understand if symptoms of depression are expressed differently and if this expression might impact the generalizability of clinical trial results.

Methods: Data was analyzed from an international multi-site depression treatment study using the HAMD-17 as the primary endpoint (n=300). Data was analyzed using SPSS v 21.0 with means and standard deviations for total and item scores at each visit computed. Effect size and Cohen's d for total scores and individual items were also calculated to determine whether differences across cultural regions were present.

Results: There were no meaningful differences in total HAMD scores at screening and though there were significant differences on the psychomotor retardation item with the Eastern Europe/Russia region observing higher severity and significantly less severity on the suicide item. Total change scores at the endpoint visit were not meaningfully different across regions with >30% change observed. For total scores Cohen's d ranged from .9406 (USA) to 1.300 (Russia) with effect size r ranging from .43 (USA) to .54 (Russia).

Conclusions: Total scores and measures of change magnitude across time suggested remarkable consistency across regions. All participants received an active anti-depressant compound and were assessed using the HAMD-17 at regular intervals throughout the trial; therefore, the rate of change across all participants was not surprising. A larger dataset that also contained HAMD-17 scores from these regions should be obtained to determine if the consistency seen in this study is more broadly present.

**W71. CLIN301-203: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF INTERMITTENT DOSES OF CERC-301 IN THE TREATMENT OF SUBJECTS WITH SEVERE DEPRESSION DESPITE ANTIDEPRESSANT TREATMENT**

*Ronald Marcus\*<sup>1</sup>, Arifulla Khan<sup>2</sup>, Michael Liebowitz<sup>3</sup>, Eileen McNulty<sup>1</sup>, Heather Fraser<sup>1</sup>*

*<sup>1</sup>Cerecor, Inc, <sup>2</sup>Northwest Clinical Research Center, <sup>3</sup>Medical Research Network*

**Abstract:** Introduction: A great need exists for therapies that act more rapidly than currently available antidepressants. CERC-301 is a highly selective, orally bioavailable, NMDA receptor subunit 2B (NR2B), also referred to as Glutamate NMDA receptor subunit epsilon-2 (GluN2B) antagonist that is being developed as a potentially rapid acting antidepressant for adjunctive use.

Methods: Clin301-203 was a 3-week randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study of two doses of adjunctive CERC-301 (12 mg or 20 mg) or placebo, administered 7 days apart, in the treatment of subjects with MDD who have not adequately responded to antidepressant therapy, either a selective serotonin reuptake inhibitor (SSRI) or a serotonin and norepinephrine reuptake inhibitor (SNRI).

The study randomized 115 subjects in two sequential one week periods with the efficacy results averaged across the periods. Placebo non-responders in Period 1 were re-randomized to either study drug or placebo in Period 2. The primary endpoint was change from baseline in Bech-6 averaged between 2 and 4 days post treatment. The Bech-6 scale is a subscale of the Hamilton Depression Ratings Scale (HDRS-17) believed to be more sensitive to rapid changes in depressive symptoms. Pre-specified secondary endpoints include change from baseline in Bech-6, HDRS-17, Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR), and Clinically Useful Depression Outcome Scale-Anxiety Self Report (CUDOS-SR) at various time points after study drug administration.

Results: The mean improvement from baseline on the Bech-6 scale averaged over Days 2 and 4 post treatment (primary endpoint) for Period 1 was 3.82 for placebo, 2.50 for the 12 mg dose and 4.11 for the 20 mg dose, and for Period 2 was 2.86 for the placebo, 1.64 for the 12 mg dose and 3.38 for the 20 mg dose. The weighted average for the difference in placebo and drug improvement (placebo minus drug) was +1.45 and -0.04 for 12 mg and 20 mg CERC-301, respectively and were not statistically significant.

In a pre-specified analysis of the mean improvement from baseline on the Bech-6 at Day 2 for Period 1 was 3.59 for placebo, 4.71 for 20 mg; and for Period 2, 2.30 for placebo and 3.52 for 20 mg. In another pre-specified analysis of the mean improvement from baseline on the HDRS-17 at Day 2 for Period 1 was 6.24 for placebo and 9.71 for 20 mg; and for Period 2, 3.60 for placebo and 5.38 for 20 mg. Although not statistically significant, these changes at Day 2 after dosing are considered clinically meaningful. Study results on the self-report scales QIDS-SR and CUDOS-SR were also not statistically significant but were numerically in favor of CERC-301 20 mg over placebo.

Consistent with previous trials, CERC-301 was generally well-tolerated with no SAEs reported and no discontinuations due to AEs. The most commonly reported adverse events in the study were increased blood pressure, dizziness, somnolence and paresthesia. Blood pressure changes were transient in nature and increases were not dose-related.

Conclusions: CERC-301 (12 mg or 20 mg) was evaluated in subjects with MDD not currently adequately treated with an anti-depressant using an SPCD design. Although CERC-301 did not achieve its primary endpoint, data suggest a possible anti-depressant benefit two days post-dose. CERC-301 was generally well-tolerated. Further studies are warranted to evaluate different dosing regimen (higher dose; twice a week dosing) to maximize the efficacy of CERC-301.

## **W72. MARIJUANA - IS IT A MEDICINE**

*Thersilla Oberbarnscheidt, Maryam Davari\**

**Abstract:** Marijuana is the most commonly used illicit substance in the United States and worldwide. The smoking of marijuana is an increasingly observed phenomenon in the adolescent population and even more common nowadays than cigarette smoking. A special focus should therefore aim to the effects of marijuana in that particular age group.

Adolescents are particularly vulnerable to the effects of marijuana because their brain and neuro-circuits are still developing. The exposure of marijuana to the still pruning brain causes not only short-term cognitive impairment but also permanent, life-long reduction in their cognitive abilities. This is due to marijuana's effect on processing speed and a reduction in gray matter in several brain regions as well as a decrease in white matter.

Marijuana is viewed as a "gateway" drug and more so than adults, the adolescents are at higher risk to develop a subsequent drug addiction after the exposure to marijuana (4). A positive correlation between the age of first exposure to marijuana and the development for an addiction to other drugs has been shown.

There is also a strong association between the onset of other psychiatric disorders, for example bipolar disorder, psychosis, depression and anxiety and even suicidal ideations in context with the use of marijuana.

This article is a systematic literature review of the current scientific literature regarding the indications, toxic effects and pathological evidence from the use of marijuana in the adolescents.

### **W73. LAUFLUMIDE (R)-(-)- (NLS-4): A NEW POTENT WAKE-PROMOTING AGENT**

*Gianina Luca, Mehdi Tafti\**

*University of Lausanne*

**Abstract:** Psychostimulants are used for the treatment of excessive daytime sleepiness in a wide range of sleep disorders as well as in several other conditions such as attention deficit hyperactivity disorder or cognitive impairment in neuropsychiatric disorders. With increasing number of patients there is an increasing interest and need for wake-promoting drugs with high efficacy and low side effects. Here, we have tested in mice the wake-promoting properties of NLS-4, its effects on the following sleep and its pharmacological effects as compared with those of modafinil and placebo.

NLS-4 at 64mg/kg induced significantly longer wakefulness duration than modafinil at 150mg/kg. Although no significant sleep rebound was observed after both treatments as compared with placebo, modafinil-treated mice showed significantly more NREM sleep when compared to NLS-4. Spectral analysis of the NREM EEG indicated an increased power density in delta activity (1-4 Hz) during sleep after NLS-4 treatment as compared to both placebo and modafinil. Also, time course analysis of the delta activity showed a significantly longer increase in power density in NLS-4-treated mice as compared to modafinil. Our results indicate that NLS-4 is a highly potent wake-promoting drug, with no sign of hypersomnia rebound. Interestingly, as opposed to modafinil, recovery sleep after treatment with NLS-4 is characterized by higher sleep intensity (higher delta activity) more than higher amount of sleep.

#### **W74. A NOVEL VASOPRESSIN 1A RECEPTOR ANTAGONIST IN PHASE II DEVELOPMENT FOR MULTIPLE DISORDERS OF STRESS, MOOD, AND BEHAVIOR**

*Neal Simon\*<sup>1</sup>, Michael Brownstein<sup>1</sup>, Shi-fang Lu<sup>1</sup>, Christophe Guillon<sup>1</sup>, Ned Heindel<sup>2</sup>*

*<sup>1</sup>Azevan Pharmaceuticals, Inc., <sup>2</sup>Lehigh University*

**Abstract:** SRX246 is a first-in-class, high affinity, high selectivity, vasopressin 1a (V1a) receptor antagonist that is orally bioavailable and crosses the blood-brain barrier. The compound, which is being developed by Azevan Pharmaceuticals, Inc., represents a novel mechanism of action for treating disorders of stress, mood, and behavior. SRX246 is in Phase II clinical trials for three psychiatric indications with major unmet need. An Exploratory Phase II trial for the treatment of Intermittent Explosive Disorder (NCT0205563) was completed in Q2 2016. The primary endpoint and exploratory goals of the trial were achieved. SRX246 was generally well tolerated and no serious adverse events were reported. Adverse events were mild, transient, and not dose-dependent. The exploratory analyses revealed statistically significant differences favoring SRX246 in key outcome measures that indicate clinical benefit. Additional Phase II trials are in progress, one for the treatment of irritability in Huntington's Disease patients (NCT02507284; supported by the NIH NeuroNext program and under the purview of the Psychiatry Division at the FDA), and the other for the treatment of PTSD (NCT02733614; supported by the Dept. of Defense). The status of these trials will be presented. These Phase II clinical trials were based on preclinical studies in animal models and translational experimental medicine fMRI findings in humans. The former showed that SRX246 reduces measures of fear, aggression, depression, anxiety, and stress. Additional neuroimaging and behavioral investigations demonstrated that SRX246 selectively blocks stress, arousal, and fear in social interaction and conditioned fear models without impacting other behaviors. Translational results in humans established that SRX246 is active in the CNS and that it significantly attenuates vasopressin-induced effects in brain regions involved in stress-related disorders.

Financial support: The development of SX246 at Azevan Pharmaceuticals has been supported by the National Institutes of Health through multiple SBIR grants from NIMH, the National Toxicology Evaluation Program, the Rapid Access to Interventional Development (RAID) Program, the NINDS NeuroNext program; through a grant from the Dept. of Defense; and private venture capital.

#### **W75. BRAIN NEUROCHEMISTRY IN UNMEDICATED OBSESSIVE COMPULSIVE DISORDER PATIENTS AND EFFECTS OF 12-WEEK ESCITALOPRAM TREATMENT: A 1H-MAGNETIC RESONANCE SPECTROSCOPY STUDY**

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**Abstract:** Background. Obsessive compulsive disorder (OCD) is one of the most common psychiatric disorder yet its pathophysiology is not very clear. Many studies have been



conducted to identify neurobiology of obsessive compulsive disorder. Imaging studies done over the last few decades have suggested the role of cortico-striato-thalamo-cortical (CSTC) circuitry in the pathophysiology of OCD and have broadly implicated three brain regions namely head of caudate nucleus, cingulate cortex and medial thalamus. MRS is considered to be a sensitive measure of treatment effects on neurological processes in the pathophysiology of disorders. Only a few studies are available on treatment-related responses in neurochemicals assessed by magnetic resonance spectroscopy (MRS).

**Aims and Objectives.** To measure the levels of NAA (N-Acetyl Aspartate), total Choline (tCho), myo-Inositol (mI), Glutamate+Glutamine (Glx) and total Creatine (tCr) in three regions of interest (ROI: caudate nucleus, anterior cingulate cortex and medial thalamus) in currently unmedicated OCD patients before and after treatment with escitalopram and to compare the levels of these neurochemicals in the three ROI between patients with OCD and healthy controls and ROI in OCD patients before and after treatment.

**Methods.** In the present study, we included subjects diagnosed with OCD (n=28) with a total duration of illness <5 years as a study group and matched healthy controls (n=26). The inclusion criteria for OCD group was: right-handed individuals, aged >18 years, not on any specific treatment for OCD for last >8 weeks with no other psychiatric comorbidity. A pre-post and case-control design was employed in which OCD patients underwent 1H-MRS at baseline (before starting any treatment) and 12 weeks after treatment with escitalopram (n=21). Clinical assessment was carried out using a semi-structured proforma, Yale-Brown obsessive compulsive scale (YBOCS) and World Health Organization – Disability Assessment Scale 2.0 (WHO-DAS 2.0) before as well as after treatment. Volume localised 1H-MR spectroscopy was carried out at 3 Tesla Philips MR scanner. User-independent frequency domain fitting program (LC Model) version 6.1-4A having a basic set of model metabolites was used to determine the absolute concentration of metabolites.

**Results.** Our data suggested higher levels of Myo-inositol (mI), total Choline (tCho) and Glx (Glutamate+Glutamine) in medial thalamus at pre-assessment in OCD subjects (as compared to controls) and a significant reduction in tCho and Glx after treatment. In the caudate nucleus, myo-inositol level was positively correlated with disorder severity ( $r=0.603$ ,  $p<0.05$ ). In the anterior cingulate, Glx level was positively correlated with disease severity ( $r=0.490$ ,  $p<0.01$ ). While, in medial thalamus, level of tCho ( $r= -0.575$ ,  $p<0.05$ ) was negatively correlated with disorder severity. In the medial thalamus, a decrease in tCho level with treatment was associated with decrease in disorder severity ( $r=0.538$ ).

**Conclusion.** Our study replicates the findings of hyper glutaminergic state (as suggested by increased Glx levels) and neurodegeneration (as suggested by increased tCho and mI in thalamus) in CSTC circuitry in patients with OCD suggested by previous studies using MRS as well as other functional imaging studies. Our study also highlights the potential reversibility of the neurochemical abnormalities seen in OCD patients with treatment.

**Thursday, June 1, 2017**

## Poster Session II

### **T1. FORMAL CARDIAC SCREENING PRIOR TO INITIATING STIMULANT MEDICATION IN ADHD CHILD AND ADOLESCENT MINORITY POPULATION: A DUAL ASSESSMENT IN AN INNER-CITY TEACHING OUTPATIENT CLINIC**

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**Abstract:** Background: Millions of children and adolescents are diagnosed with ADHD and treated with stimulant medications. Although the association between stimulant medications and cardiac sudden death remains inconclusive, a careful cardiac screening is still recommended by important professional organizations to identify kids at risk for lethal outcome. Our study aims to examine the practice of evaluating pre-stimulant treatment cardiac status by trainees in a teaching child & adolescent psychiatry outpatient clinic.

Methods: Cardiac screening related literature was reviewed. A dual assessment, using chart (EHR) review and prescriber survey, was conducted. 75 medical records that contained initial psychiatric evaluations conducted by trainees (child psychiatry fellows and general psychiatry residents) in the last academic year were reviewed. We selected 25 charts based on our primary search terms ADHD diagnosis, stimulant medications and cardiac (personal and family) screening. To support our goal, we used two tools: a modified form of AACAP Performance in Practice Tool for Retrospective Chart Review of Initial Evaluation of Pediatric Patients Diagnosed with ADHD and a Brookdale Provider Survey focusing on the cardiac screening among child and adolescent psychiatry fellows and general psychiatry residents.

Results: Out of the 25 thoughtfully reviewed charts, only two (8%) charts formally documented a cardiac screening but without specific details. Most charts (84 - 96 %) recorded the family and/or personal cardiac history to a certain degree. We concurrently invited the same EHR prescribers (10 trainees - 6 child psychiatry fellows and 4 PGY 3 general psychiatry residents) to respond to our questions that followed the EHR reviews on this studied matter. The majority of participants (80 - 100 %) gave positive responses when it came to 'cardiac screening' and ECG, but more than half of them (60%) indicated some or no formal documentation during their clinic evaluations. We identified several discrepancies between the trainee reports and the EHR review. 40 % of respondents endorsed appropriate documentation and approximately 70 - 80 % of participants claimed they asked detailed questions about personal and family cardiac history compared to only 8 % that were found to be in partial compliance on these two items during chart review. Potential reasons for insufficient documentation (e.g. time consuming or "I discussed the subject at large with them; do I need to put it in writing") were explored and possible solutions (e.g. EHR smart text, well-defined training) were identified.

Conclusions: While most trainees in this study were conducting cardiac history review in their practice, a formal screening instrument (e.g. questionnaire) and proper documentation were lacking. A well-defined and cohesive curriculum in conducting as well as documenting cardiac screening is deemed necessary for our trainees. Research to further examining the effectiveness of any proposed recommendations is anticipated.

### **T2. EFFICACY AND SAFETY OF HLD200, A NOVEL DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE FORMULATION, IN**

## CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: RESULTS FROM A PIVOTAL PHASE 3 TRIAL

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**Abstract:** Background: Long-acting methylphenidate (MPH) formulations are recommended as first-line therapy for youth with attention-deficit/hyperactivity disorder (ADHD) and are given once daily in the morning to reduce ADHD symptoms for up to 12 hours (1). However, many have delays in the initial onset of action of up to 2 hours after dosing, leaving a significant portion of the early morning with inadequate ADHD symptom control (1). There remains a significant unmet need in stimulant-treated youth with ADHD to provide clinically meaningful early morning control of ADHD symptoms, and to improve impairments in early morning functioning from the time of awakening until school or other morning activities without compromising functioning throughout the day and into the evening (2). Evening-dosed HLD200 delays the initial release of MPH by approximately 8-10 hours, targeting the onset of clinically meaningful treatment effect upon awakening and lasting into the evening. The objectives of this study were to: (i) determine whether HLD200 improves control of ADHD symptoms and at-home early morning and late afternoon/evening functional impairments versus placebo in children with ADHD; and (ii) evaluate the safety and tolerability of HLD200. Methods: This was a pivotal, randomized, double-blind, multicenter, placebo-controlled, phase 3 trial of HLD200 in children (6-12 years) with ADHD (NCT02520388). Subjects had current or prior response on MPH. Following a screening period of  $\leq 2$  weeks with a 3- to 7-day washout, subjects were randomized (1:1) to HLD200 or placebo once-daily each evening for 3 weeks. After 1 week, the initial 40 mg dose of HLD200 was titrated in 20-mg weekly increments to 60 mg and 80 mg, as tolerated, with a one-step down-titration permitted. The primary efficacy measure was the ADHD Rating Scale (ADHD-RS-IV) Total Score following 3 weeks of treatment. The key secondary efficacy measures were the Before School Functioning Questionnaire (BSFQ) and Parent Rating of Evening and Morning Behavior-Revised, Morning (PREMB-R AM) and Evening (PREMB-R PM) subscales following 3 weeks of treatment. Safety measures included treatment-emergent adverse events (TEAEs), with a focus on sleep and appetite.

Results: Of 163 children enrolled across 22 sites, 161 were included in the intent-to-treat population. After 3 weeks of treatment, children on HLD200 versus placebo achieved a significant improvement in ADHD symptoms (least squares [LS] mean ADHD-RS-IV: 24.1 vs 31.2;  $P=0.002$ ), at-home early morning functioning (LS mean BSFQ: 18.7 vs 28.4;  $P<0.001$ ; LS mean PREMB-R AM: 2.1 vs 3.6;  $P<0.001$ ), and at-home late afternoon/evening functioning (LS mean PREMB-R PM: 9.4 vs 12.2;  $P=0.002$ ). No serious TEAEs were reported, and only 1 subject on HLD200 (1.2%) and 4 subjects on placebo (5.0%) had TEAEs leading to early withdrawal. The most common TEAEs ( $\geq 10\%$ ) reported by children on HLD200 were decreased appetite and insomnia. Sleep-related TEAEs were mild or moderate in severity and most were transient (96.6% resolved within the study).

Conclusions: Evening-dosed HLD200 was well tolerated and demonstrated significant improvements in not only ADHD symptoms, but also in both at-home early morning and late afternoon/evening impaired functioning versus placebo in children with ADHD. To our

knowledge, this is the first study to demonstrate significant improvements in both early morning and late afternoon/evening impaired functioning with a single dose of a long-acting stimulant in children with ADHD.

### **T3. STIMULANT MEDICATION VERSUS BEHAVIORAL PARENT TRAINING EFFECTS ON MOTHERS WITH ADHD**

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**Abstract:** ADHD is highly familial and children with ADHD often have parents with ADHD. ADHD in mothers is often unrecognized and untreated. We sought to compare the effects of a long acting stimulant medication with behavioral parent training on ADHD symptom dimensions (DSM -V, Wender Utah Criteria) in a sample of mothers with untreated ADHD who have young children with elevated ADHD symptoms.

Mothers (n = 35) who met diagnostic criteria for ADHD were randomized to either 8-weeks of individually titrated Maternal Stimulant Medication (MSM) (Lisdexamphetamine) (n = 18) or behavioral parent training (n = 17) utilizing Barkley's Defiant Children as a model. The primary outcome was the Conners Adult ADHD rating scale completed by the mothers. Secondary outcomes include the Clinical Global Impressions-Severity and Improvement completed by a rated blinded to treatment assignment, Wender-Reimherr Adult ADHD Scale (WRAADS), and the Barkley Functional Impairment Rating Scale (BFIS). Unlike previous adult ADHD clinical trials, concurrent antidepressant and anti-anxiety medication were allowed.

Lisdexamphetamine (mean dose 42.5, range 20-70) was well tolerated, 1 patient discontinued and 1 switched to methylphenidate due to inadequate response. Compared to behavioral parent training, MSM was associated with significant improvements in CAARS Inattention ( $p < .001$ ), ADHD index ( $p < .001$ ). Clinicians rated the MSM group as more improved on CGI-I ( $p < .001$ ), and lower on CGI-S ( $p < .05$ ) and WRAADS Disorganization ( $p < .001$ ). There were no differences on the BFIS.

The results indicate that maternal stimulant medication was well tolerated in this population and associated with improvements in ADHD symptoms relative to behavioral parent training. However, most parents were moderately impaired despite symptomatic improvement after 8 weeks of treatment. Limitations include the small sample size, and a sample that was relatively homogenous in terms of ethnicity and social economic class. In addition, there was no placebo and although mothers were getting an active treatment the focus of the treatment was on improving parent-child interactions. Future studies are underway targeting multiplex families where both the child and parent have ADHD and exploring how to sequence and combine behavioral and pharmacological treatments.

### **T4. EFFECT OF BASELINE INFLAMMATORY BIOMARKER (HS-CRP) ON RESPONSE TO LURASIDONE TREATMENT IN PATIENTS WITH BIPOLAR DEPRESSION: AN EXPLORATORY ANALYSIS**

*Charles Raison<sup>2</sup>, Andrei Pikalov<sup>\*1</sup>, Cynthia Siu<sup>3</sup>, Ken Koblan<sup>1</sup>, Antony Loebel<sup>1</sup>*

**Abstract:** Objectives: Bipolar depressive episodes are more common and challenging to treat than mania or hypomania in bipolar disorders, however, the pathophysiology of bipolar depression is not well understood. As is the case with unipolar depression, bipolar depression is associated with elevated levels of c-reactive protein (CRP). While elevated CRP has been associated with a poorer response to standard antidepressant therapy, Raison et al. (2013) showed that tumor necrosis factor (TNF) antagonism (using infliximab) improved depressive symptoms in patients with treatment-resistant depression (TRD) and high baseline hs-CRP, while not benefiting patients with TRD and lower levels of CRP. The objective of the current study was to evaluate the impact of pre-treatment levels of CRP on response to lurasidone in the treatment of bipolar depression.

Methods: The analysis population included all outpatients who met DSM-IV-TR criteria for bipolar I depression and received randomized, double-blind, monotherapy treatment with lurasidone (N=166 for 20-60 mg/day, or N=170 for 80-120 mg/day) or placebo (N=170) for 6 weeks (Loebel et al., 2014). Primary efficacy endpoint was change from baseline to week 6 in severity scores on the Montgomery Åsberg Depression Rating Scale (MADRS). Levels of inflammation were measured by hs-CRP. Analysis of covariance and statistical interaction tests were applied to investigate the moderating effects of hs-CRP level, with terms for treatment, baseline score, center, hs-CRP level and hs-CRP-by-treatment effect.

Results: A total of 118 (24.5%) patients had a high level of hs-CRP (>5.0 mg/L) prior to treatment. Baseline hs-CRP levels were not associated with pre-treatment MADRS scores ( $P > 0.05$ ). The statistical interaction between treatment and log-transformed baseline hs-CRP level was significant for change in MADRS from baseline to week 6 study endpoint, with a larger placebo-corrected effect size (Cohen's  $d=0.81$ ) favoring lurasidone patients with baseline hs-CRP >5 mg/L compared to Cohen's  $d=0.33$  for lurasidone patients with baseline hs-CRP  $\leq 5$  mg/L. There were significant interactions between lurasidone treatment and log-transformed baseline hs-CRP for the following MADRS items: "reduced appetite", "lassitude", "apparent sadness", "reported sadness", and "pessimistic thoughts" (all  $P < 0.05$ ), with improvement in these symptoms all favoring lurasidone patients with higher baseline hs-CRP level.

Conclusion: Our findings, based on the results of a placebo-controlled trial, suggest that baseline levels of hs-CRP predict therapeutic efficacy of lurasidone for the treatment of bipolar depressive symptoms, with larger effect sizes observed in patients with elevated levels of the inflammatory marker hs-CRP at study baseline. These findings require prospective confirmation, but suggest that the efficacy of lurasidone in patients with bipolar depression may in part be associated with anti-inflammatory effects. If confirmed in future studies, they may also point toward CRP as being a predictive biomarker that will enhance our ability to develop precision medicine approaches in the use of lurasidone for the treatment of bipolar depression.

## **T5. ABNORMAL FEAR CIRCUITRY IN ADHD: A CONTROLLED MAGNETIC RESONANCE IMAGING STUDY**

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**Abstract:** Introduction: Attention Deficit/Hyperactivity Disorder (ADHD) is a common, early onset, treatable neurobiological disorder associated with high morbidity and dysfunction. A recent meta-analysis documented a robust and bidirectional association between ADHD and PTSD in both referred and non-referred samples of adults and children. Because the onset of ADHD was consistently earlier than the onset of PTSD in all studies examining temporality, we hypothesized that ADHD may be an antecedent risk factor for PTSD and thus associated with a neurobiological vulnerability for PTSD.

The goal of this study was to examine whether individuals with ADHD have abnormalities in fear circuitry resembling those found in PTSD. We studied medication naïve young adults with and without ADHD with no history of trauma exposure using a validated fear conditioning and extinction neuroimaging paradigm. We hypothesized that nontraumatized, medication-naïve subjects with ADHD would demonstrate dysfunctional activation in brain structures that mediate fear extinction and learning, consistent with those previously reported in subjects with PTSD.

Methods: A total of 27 (13 male and 14 female) non-traumatized, right-handed, medication-naïve, young adult subjects age 19-33 (M = 23, SEM = 1) with ADHD were compared to 20 (10 male and 10 female) non-traumatized, right-handed healthy controls (HC) age 21-34 (M = 26, SEM = 1). ADHD subjects were recruited from referrals to an adult ADHD program at Massachusetts General Hospital and through media advertisements. Controls were recruited from the community and free of current psychiatric disorders. All ADHD subjects were diagnosed with childhood-onset and persistent DSM-IV-TR.

Participants underwent a 2-day fear conditioning and extinction paradigm in a 3-T fMRI scanner. The protocol was identical to one previously developed and validated in healthy subjects and clinical populations including PTSD, OCD, and schizophrenia. Conditioning and extinction training were conducted on day 1. Extinction recall was conducted on day 2. Skin conductance response (SCR) was obtained as an index of the conditioned response.

Results: Compared to healthy controls, ADHD subjects had significantly greater insular cortex activation during early extinction, lesser dorsal anterior cingulate cortex (dACC) activation during late extinction, lesser activation in ventromedial prefrontal cortex (vmPFC) during late extinction learning and extinction recall, and lesser activation in hippocampus during extinction recall. Hippocampal and vmPFC deficits were similar to those documented in PTSD subjects compared to traumatized controls without PTSD.

Conclusion: Non-traumatized, medication naïve adults with ADHD had abnormalities in fear circuits during extinction learning and extinction recall consistent with those previously documented in subjects with PTSD compared to traumatized controls without PTSD. These findings, if confirmed in future studies, would support the hypothesis of a neurobiological vulnerability to PTSD in ADHD and help explain the significant association between ADHD and PTSD.

## **T6. DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE NOVEL THERAPEUTIC AEVI-001 IN ADOLESCENTS WITH ADHD AND GLUTAMATERGIC NETWORK GENE MUTATIONS**

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<sup>1</sup>*Aevi Genomic Medicine, <sup>2</sup>Johns Hopkins University and Kennedy Krieger Institute*

**Abstract:** Objective: Loss-of-function mutations (copy number variations, CNVs) in metabotropic glutamate receptors (GRMs) and related genes have been identified in ~20% of children/adolescents with ADHD, representing a population in which glutamatergic dysfunction may play a key role in ADHD pathogenesis. Children/adolescents with mutation-positive ADHD (GRM+ ADHD) may be candidates for glutamate-modulating therapy. We will report results of a Phase 2 study evaluating the efficacy and tolerability of the glutamate modulator AEVI-001 in adolescents with moderate severity GRM+ ADHD.

Methods: Phase 2 randomized, double-blind, placebo-controlled, parallel-group study of 6-week duration in subjects 12-17 yrs of age with moderate severity ADHD (baseline ADHD-RS-5 score:  $\geq 28$  without conventional ADHD therapy) and GRM biomarker-positive genotype (GRM+ ADHD). All ADHD medications were discontinued with appropriate washout period before randomization. 4-wk dose optimization period: 100-mg b.i.d. starting dose increased at weekly intervals based on clinical response to maximal dose of 400 mg b.i.d. Optimized dose (100 mg, 200 mg, or 400 mg b.i.d.) was maintained 2 weeks.

Results: 101 subjects were randomized 1:1 to placebo or study drug. Baseline characteristics: male, 63%; median age, 14 yrs; median age at ADHD diagnosis, 6 yrs; median years since ADHD diagnosis, 7 yrs; ADHD presentation: inattentive, 29%; hyperactive/impulsive, 2%; combined, 69%. Median Baseline CGI-S score, 4. Mean Baseline ADHD-RS-5 score, 38 (range 12 – 54). Efficacy and tolerability/safety results to be presented, including primary endpoint (ADHD-RS-5 total score change from Baseline to end of treatment as LOCF analysis) and secondary endpoint (number and percent of subjects “Improved” vs. “Not Improved”). Analyses will also include % patients meeting responder criteria defined as  $\geq 30\%$  change from Baseline ADHD-RS-5 or CGI-I score of 1 or 2.

Conclusion: Subject characteristics were consistent with expectations. Efficacy and safety/tolerability results will be presented. Study sponsored by Aevi Genomics Medicine.

## **T7. DYSREGULATION OF THE HISTONE DEMETHYLASE KDM6B IN ALCOHOL DEPENDENCE IS ASSOCIATED WITH EPIGENETIC REGULATION OF INFLAMMATORY SIGNALING PATHWAYS**

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**Abstract:** Epigenetic enzymes oversee long-term changes in gene expression by integrating genetic and environmental cues. While there are hundreds of enzymes that control histone and DNA modifications, their potential roles in substance abuse and alcohol dependence remain underexplored. A few recent studies have suggested that epigenetic processes could underlie transcriptomic and behavioral hallmarks of alcohol addiction. In the present study, we sought to identify epigenetic enzymes in the brain that are dysregulated during protracted abstinence as a consequence of chronic and intermittent alcohol exposure. Through highly quantitative mRNA expression analysis of over 100 epigenetic enzymes, we identified 11 that are significantly altered in alcohol dependent rats compared to controls. Follow up studies of one of these enzymes, the histone demethylase KDM6B, showed that this enzyme exhibits region-specific dysregulation in the prefrontal cortex and nucleus accumbens of alcohol dependent rats. KDM6B was also upregulated in human alcoholic brain. Upregulation of KDM6B protein in alcohol dependent rats was accompanied by a decrease of tri-methylation levels at histone

H3, lysine 27 (H3K27me3), consistent with the known function of KDM6B. ChIP-sequencing analysis showed that alcohol-induced changes in H3K27me3 were significantly enriched at genes in the IL-6 signaling pathway, consistent with the well-characterized role of KDM6B in modulation of inflammatory responses. Knockdown of KDM6B in cultured microglial cells diminished IL-6 induction in response to an inflammatory stimulus. Our findings implicate a novel KDM6B-mediated epigenetic signaling pathway that crosstalks with inflammatory signaling pathways that are known to underlie the development of alcohol addiction.

## **T8. EPIGENETIC MECHANISMS IN ALCOHOL USE DISORDER QUANTIFIED BY NON-INVASIVE PET IMAGING**

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**Abstract:** Effective treatment and prevention of alcohol use disorder (AUD) remains a major health issue due to our limited understanding of the underlying pathophysiology and neurocircuitry changes necessary for successful therapy. In the past decade, research on epigenetics has revealed that AUD may have a strong connection with dysfunction of chromatin-modifying enzymes, and among them, histone deacetylases (HDACs) are frequently implicated. The rodent studies have demonstrated that the treatment with ethanol in rodents could upregulate the histone acetylation levels in several brain regions, such as prefrontal cortex. In addition, several HDAC isoforms, such as HDAC2 and HDAC3, are reported to increase as the treatment of ethanol in human neuronal cell line or in amygdala. The pan-HDAC inhibitors, trichostatin A (TSA) and sodium butyrate, as well as class I selective HDAC inhibitor (MS-275), have been tested in animal models. The treatment of these HDAC inhibitors could reverse ethanol-induced tolerance, anxiety, and ethanol drinking with upregulated histone acetylation level in the amygdala of rats. The treatment could reduce ethanol-induced behaviors and diminished the motivation to consume ethanol as well.

HDACs, therefore, hold a great potential as therapeutic targets and the investigation on HDAC expression changes in the development of AUD will directly advance understanding of the importance of epigenetic role in the neurobiology of AUD. As a critical next step, a key goal of this proposal is to measure HDAC density and distribution in AUD patients in vivo as a function of sex. Until recent developments from our lab, the density and distribution of HDAC in the brain could not be quantified without sampling tissue.

The first radiotracer, [11C]Martinostat, for non-invasive HDAC imaging in humans via positron emission tomography (PET) from our lab was recently approved by the FDA for first-in-man studies (IND # 123154). Our lab has now successfully imaged healthy adults (18-65 years old) using [11C]Martinostat. The imaging data are quite promising and are already providing insights into regional HDAC expression. These data represent a major step forward in understanding epigenetic mechanisms in vivo.

We hypothesize that changes in HDAC enzyme expression in AUD can be mapped visually and quantitatively within the living brain by PET. In this abstract, we will report our progress on measuring HDAC density and distribution in the human brain using a unique brain-specific simultaneous magnetic resonance (MR) and PET scanner with [11C]Martinostat, which will deliver answers to fundamental questions about chromatin modifying enzymes in the human brain in a way that has not been possible until now.



**T9. LOW-DOSE BEDTIME SUBLINGUAL CYCLOBENZAPRINE (TNX-102 SL\*) FOR THE TREATMENT OF MILITARY-RELATED PTSD: RETROSPECTIVE ANALYSES OF THE MEDIATORS AND MODERATORS OF TREATMENT RESPONSE**

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**Abstract:** Background: Study TNX-CY-P201 ('AtEase Study') was a Phase 2 efficacy and safety trial of TNX-102 SL for PTSD in a military-related PTSD sample. TNX-102 SL is a sublingual tablet formulation of low dose cyclobenzaprine designed for bedtime administration and rapid sublingual absorption, which bypasses first-pass metabolism and has desirable parent and major metabolite pharmacokinetic profiles. Cyclobenzaprine, a unique tricyclic molecule, has potent 5-HT<sub>2A</sub> serotonergic,  $\alpha$ 1-adrenergic, and H<sub>1</sub>-histaminergic receptor blocking properties in receptor binding studies. TNX-102 SL is hypothesized to improve global symptoms of PTSD through therapeutic effects on sleep disturbance and hyperarousal. The analyses to be presented explored moderators and mediators of treatment response to TNX-102 SL.

Methods: AtEase was a 12-week, double-blind, placebo-controlled, randomized multicenter trial in males and females, ages 18-65 years, meeting DSM-5 PTSD diagnosis as assessed by Clinician Administered PTSD Scale for DSM-5 (CAPS-5). Participants were randomized at 24 US sites to TNX 2.8 mg (1 x TNX-102 SL 2.8 mg tablet), TNX 5.6 mg (2 x TNX-102 SL 2.8 mg tablets) or placebo in a 2:1:2 ratio. Eligible participants had experienced Criterion A-qualifying trauma(s) during military service since 2001, had at least moderate PTSD severity (CAPS-5 score  $\geq 29$ ), and were free of antidepressants for >2 months and free of or washed off other psychotropics. Exclusions included serious suicide risk, unstable medical illness, substance use disorders within 6 months, and lifetime history of bipolar, psychotic, obsessive-compulsive, or antisocial personality disorders. The primary efficacy analysis was the mean change from baseline (MCFB) in CAPS-5 score between TNX 2.8 mg and placebo. Secondary analyses included MCFB in CAPS-5 between TNX 5.6 mg and placebo, and group comparisons on the Clinical Global Impression-Improvement scale, Sheehan Disability Scale, PROMIS Sleep Disturbance, and CAPS-5 clusters.

Results: A total of 245 participants were enrolled in 2015. Although the primary efficacy analysis comparing TNX 2.8 mg (n=90) to placebo (n=92) was not significant, the TNX 5.6 mg (n=49) group demonstrated a strong trend towards greater MCFB improvement in CAPS-5 at Week 12 (p=0.053, MMRM; effect size=0.36). Sensitivity analyses showed significantly greater improvement in total CAPS-5 with TNX 5.6 mg compared with placebo. Improvements in sleep and hyperarousal occurred early (by Week 2) and appeared to mediate therapeutic response. Moderator analyses indicated those with combat trauma subtype (85%) and greater baseline CAPS-5 severity scores were those who responded most robustly to TNX 5.6 mg. The most common adverse event (AE) in the TNX-102 SL arms was tongue numbness (39% in TNX 2.8 mg; 36% in TNX 5.6 mg), which was generally transient (<1 hour), and never rated as severe. Systemic AEs of somnolence, sedation, headache appeared dose-dependent; rates in TNX 5.6 mg were 16%, 12%, 12%, respectively.

Discussion: TNX 5.6 mg demonstrated activity over placebo in this multicenter trial in military-related PTSD, heretofore considered a population difficult to treat with pharmacotherapies. This talk will focus on the retrospective analyses indicating treatment

response was mediated by primary effects on sleep and arousal, and that moderators of treatment response included combat trauma subtype and higher CAPS-5 baseline. Discussion will also address how these analyses supported advancement of TNX 5.6 mg to Phase 3 testing for PTSD (the “HONOR Study,” currently ongoing).

Trial Registration: NCT02277704

\*TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

#### **T10. A PHASE IB DOSE RANGING STUDY OF DIRECT NOSE TO BRAIN DELIVERY OF NEUROPEPTIDE Y IN PATIENTS WITH POSTTRAUMATIC STRESS DISORDER**

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**Abstract:** Background: Anxiety and trauma-related disorders are among the most prevalent and disabling medical conditions in the U.S., and posttraumatic stress disorder (PTSD) in particular exacts a tremendous public health toll. We examined the tolerability and anxiolytic efficacy of neuropeptide Y (NPY) administered via an intranasal route in patients with PTSD. Methods: This randomized, cross-over, dose-ranging study enrolled 24 individuals according to an escalation algorithm into one of five dose cohorts as follows: 1.4 mg (n=3), 2.8 mg (n=6), 4.6 mg (n=5), 6.8 mg (n=6), and 9.6 mg (n=6). Each individual was dosed with NPY/placebo on separate treatment days one week apart in random order under double-blind conditions; assessments were conducted at baseline and following a trauma script symptom provocation procedure subsequent to dosing. Occurrence of adverse events represented the primary tolerability outcome. The difference between treatment conditions on anxiety as measured by the Beck Anxiety Inventory (BAI) and the State-Trait Anxiety Inventory (STAI) immediately following the trauma script represented the principal efficacy outcomes.

Results: NPY was well tolerated up to and including the highest dose. There was a significant interaction between treatment and dose; higher doses of NPY were associated with a greater treatment effect, favoring NPY over placebo on BAI score ( $F_{1,20}=4.95$ ,  $p=0.038$ ). There was no significant interaction for STAI score.

Conclusions: These data suggest that intranasal NPY is well tolerated up to 9.6 mg and may be associated with anxiolytic effects. Additional studies exploring the safety and efficacy of NPY are warranted.

#### **T11. ROLE OF SOTEROGRAM MEASURING ARTERIAL COMPLIANCE IN PSYCHIATRY**

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**Abstract:** Background: Peripheral arterial compliance is a measure of elasticity of the arteries that has been found to be a robust predictor of prevalent arteriosclerosis as well as incident stroke and myocardial infarction. Psychiatric diagnoses and second generation antipsychotics may contribute to cardiovascular risk and stroke, but effects on peripheral arterial compliance are unknown. The objectives of this study were: 1) to compare peripheral arterial compliance

in healthy male controls to male patients with psychiatric diagnoses who were treated with quetiapine or risperidone or off antipsychotics at time of testing and 2) to identify predictors of reduced PAC in subjects with psychiatric diagnoses.

**Methods:** In this cross-sectional study, the groups consisted of 63 male Veterans with mental illness taking quetiapine, risperidone, or no antipsychotics. There were 111 males in the control group. Mean thigh and calf arterial compliance among four groups were compared by ANCOVA, adjusting for body mass index and Framingham Risk Score. All patients were also compared to the control group. Compliance was measured with a computerized plethysmography device. In 77 male Veterans, calf and thigh compliance were modeled in separate linear regressions. The models were adjusted for age, race, smoking status, presence or absence of the metabolic syndrome, current treatment with a statin, diagnosis of schizophrenia or schizoaffective disorder, current antipsychotic treatment, and body mass index (BMI).

**Results:** Patients (n=63) had significantly lower arterial compliance in both thigh and calf than the controls. Arterial compliance in the calf was significantly lower in the subgroups of quetiapine (n=16) and risperidone (n=19) treated, and in unmedicated (n=28) patients than in controls. In the thigh, patients taking either quetiapine or risperidone had significantly lower arterial compliance than controls. These subgroups did not differ from each other in arterial compliance. Of the 77 subjects (mean  $\pm$  SD age of  $53.7 \pm 8.8$  years), 41 were white, 36 were black, and 27 were diagnosed with schizophrenia or schizoaffective disorder (DSM-IV criteria). Fifty participants were being treated with an antipsychotic medication, while the remaining 27 were off of antipsychotics for at least 2 months. Our model explained 27% of the variance in calf compliance. Black subjects had reduced calf compliance compared to white subjects ( $P = .02$ ). Having metabolic syndrome was associated with reduced PAC at a trend level ( $P < .08$ ), and BMI ( $P = .004$ ) and BMI<sup>2</sup> ( $P = .011$ ) were significant predictors of calf compliance. Schizophrenia versus other psychiatric diagnoses and antipsychotic treatment were not significantly associated with calf compliance.

**Conclusion:** The presence of psychiatric diagnoses is associated with reduced arterial compliance. Significant predictors of calf compliance were race (black vs white) and BMI. PAC is a noninvasive measure that may be a predictor of cardiovascular risk in psychiatric patients. Future studies are warranted to better understand the pathophysiology of PAC including but not limited to inflammation in psychiatric patients.

Soteroogram may be used more often clinically and in research studies especially with the new data that the US life expectancy has decreased for the first time since 1993.

## **T12. SUICIDE RISK PREDICTION USING MACHINE LEARNING TECHNIQUES IN SELF-REPORT VS. CLINICIAN-DERIVED DATA**

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**Abstract:** Background: Suicide is a leading cause of death worldwide and rates have been rising over the past 15 years. While we are aware of multiple factors that increase suicide risk at the group level, clinicians' judgements and psychometric tools generally show limited utility at the individual level. More accurate tools are required in order to employ targeted, cost-effective prevention strategies. Machine learning (ML) algorithms have been gaining

momentum in clinical risk prediction in the last decade, as they have demonstrated better performance as compared to standard statistical techniques in certain complex data sets (e.g. with correlated predictors that have non-linear relationships, many predictors as compared to observations, and/or the outcome is rare). Several studies have examined the performance of ML approaches in prediction of suicidality using phenotypic data and some have compared these to clinicians' judgements and logistic regression, but we are not aware of any studies that have tested the performance of these techniques in a primarily African-American population sample using self-report vs. clinician-derived data.

**Methods:** We utilized data from the Grady Trauma Project, which assesses trauma exposure in subjects seeking primary care from a large urban hospital. Subjects undergo a screening interview based on self-reported scales and are invited to participate in a clinician-administered interview for DSM-IV diagnoses obtained using the SCID and MINI. We selected predictors previously shown to be risk factors for suicide, including socio-demographic variables, the Modified PTSD symptom scale (MPSS), the Childhood Trauma Questionnaire (CTQ), the Traumatic Events Inventory (TEI), the Beck Depression Inventory II (BDI-II), and DSM IV diagnoses. We tested two commonly used ML algorithms, least absolute shrinkage and selection operator (LASSO) and support vector machines (SVM), as the former selects features during the model fitting process and the latter can fit non-linear models. Subjects with complete data were randomly divided into training (N=814, 80%) and testing (N=203, 20%) sets, each of which had 16% suicide attempters, and model parameters were estimated using 1000 iterations with balanced data combinations (i.e. equal numbers of attempters and non-attempters).

**Results:** Self-reported screening data (MPSS, CTQ, TEI, psychiatric hospitalization, and presence of physical or sexual abuse) provided reasonable sensitivity (64%) and specificity (76%). Areas Under the ROC Curve (AUC) did not differ when clinician-derived data (major depressive disorder and any psychotic disorder) was available for selection. The LASSO (AUC 0.70, CI 0.61-0.78) and SVM (AUC 0.71, CI 0.62-0.80) models did not differ substantially in predictive ability and were similar to results of previous reports of ML approaches for suicidality in different cohorts.

**Conclusions:** We describe a ML-derived algorithm for individual suicide prediction and suggest risk factors that are most relevant for prediction in an urban, primarily African-American population sample. The addition of clinician-obtained data did not improve prediction accuracy over self-reported screening data. Future work will incorporate genetic data into the models and assess for generalizability in independent cohorts.

### **T13. ARIPIRAZOLE ONCE-MONTHLY MAINTENANCE TREATMENT OF BIPOLAR I DISORDER: A BLINDED, PLACEBO-CONTROLLED, RANDOMIZED STUDY: CLINICAL EVALUATION OF BIPOLAR SYMPTOMS**

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**Abstract:** Background: Aripiprazole Once-Monthly 400 mg (AOM 400) is an atypical long-acting injectable antipsychotic. This study (NCT01567527) evaluated the efficacy and safety of AOM 400 vs placebo in preventing recurrence of mood episodes in Bipolar I Disorder (BP-I). We report the results of the secondary efficacy outcome measures which assessed bipolar symptoms during maintenance treatment with AOM 400 following stabilization of acute symptoms in patients with a manic episode.

This was a randomized-withdrawal design study in which patients' symptoms were stabilized before randomization. Therefore, patients randomized to continue on AOM 400 were expected to remain stable during the placebo-controlled phase while patients switched to placebo were expected to experience worsening of BP-I.

Methods: The study included patients aged 18-65 years who at enrollment met DSM-IV-TR criteria for BP-I and had a current manic episode with a Young-Mania Rating Scale (YMRS) total score  $\geq 20$ . Patients were stabilized on oral aripiprazole and then on AOM 400; those meeting stabilization criteria continued to a 52-week double-blind, placebo-controlled randomized withdrawal phase (maintenance treatment). Endpoints included change from time of randomization (baseline) in overall bipolar, mania, and depression severity, assessed with the Clinical Global Impressions - Bipolar Version - Severity (CGI-BP-S) scale and analyzed using a Mixed Model Repeated Measures approach. The CGI-BP - Change from preceding phase (CGI-BP-C) scale recorded improvement or worsening during each study phase and was analyzed using the Cochran-Mantel-Haenszel row mean score test; results from Last Observation Carried Forward method are reported.

Results: A total of 266 patients were randomized 1:1 to AOM 400 or placebo. Following oral and AOM 400 stabilization, the baseline mean (SD) CGI-BP-S scores for the clinical evaluation of overall bipolar and mania symptoms in the AOM 400 group were 1.7 (0.7) and 1.5 (0.7), respectively, and 1.6 (0.7) and 1.4 (0.6) in the placebo group. During the randomized phase, CGI-BP-S overall bipolar and mania scores remained stable in the AOM 400 group but worsened in the placebo group ( $p=0.022$  and  $p=0.001$  vs AOM 400 for overall and mania scores, respectively, at week 52). After stabilization, a similar pattern was seen for CGI-BP-C scores, which showed no further improvement or worsening during the randomized phase among AOM 400 treated patients, while placebo-treated patients worsened slightly ( $p<0.0001$  vs AOM 400 for both the overall and the mania scores at week 52).

CGI-BP-S depression scores (mean [SD]) were low before oral stabilization (1.6 [0.9]), before AOM 400 stabilization (1.5 [0.7]) as well as at randomization (1.5 [0.7] and 1.4 [0.7] for AOM 400 and placebo groups, respectively). CGI-BP-S and CGI-BP-C depression scores did not worsen during the stabilization phases or show any statistically significant differences between the treatments after randomization ( $p>0.53$  and  $p>0.21$  at week 52 for the two scales, respectively).

Conclusions: Patients with BP-I experiencing a manic episode showed improvements in clinically evaluated overall bipolar and mania symptom severity during stabilization on oral aripiprazole and AOM 400. Improvements seen during stabilization were maintained over 52 weeks for patients continued on AOM 400 treatment, while those switched to placebo worsened. Depression was minimal at study entry, and did not worsen during the study.

#### **T14. ARIPIPRAZOLE ONCE-MONTHLY MAINTENANCE TREATMENT OF BIPOLAR I DISORDER: A BLINDED, PLACEBO-CONTROLLED, RANDOMIZED STUDY; EFFECTS ON SYMPTOMS AND FUNCTIONING**

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**Abstract:** Background: Aripiprazole once-monthly 400 mg (AOM 400) is an atypical long-acting injectable antipsychotic. Monthly injections of AOM 400 may promote adherence and prevent recurrence of mood episodes in Bipolar-I Disorder (BP-I). This study (NCT01567527) evaluated the efficacy and safety of AOM 400 vs. placebo in preventing recurrence of mood episodes in BP-I. We report the results for secondary outcomes assessing improvements in symptoms and functioning in the maintenance treatment of BP-I after stabilization on AOM 400 following a manic episode.

Methods: The study included patients aged 18-65 years who at enrollment fulfilled DSM-IV-TR criteria for BP-I and had a current manic episode with a Young-Mania Rating Scale (YMRS) total score  $\geq 20$ . Patients who were stabilized on oral aripiprazole, then on AOM 400, continued to a 52-week double-blind, placebo-controlled randomized withdrawal phase. Endpoints measuring mood symptoms included the YMRS and the Montgomery Asberg Depression Rating Scale (MADRS) total scores. The Functioning Assessment Short Test (FAST) and the Brief Quality of Life in Bipolar Disorder (Brief QoL.BD) measured functioning. Changes from baseline (time of randomization) were evaluated using Mixed Model Repeated Measures approaches for YMRS and MADRS total scores, and analysis of covariance for FAST and Brief QoL.BD total scores (observed cases).

Results: A total of 266 patients were randomized 1:1 to AOM 400 or placebo. Following oral and AOM 400 stabilization, patients at randomization baseline were no longer manic [mean (SD) YMRS score, 2.75 (3.27)]. After randomization, those receiving AOM 400 showed little change in YMRS scores, while those on placebo worsened ( $p < 0.0016$  at Week 52). Mean (SD) MADRS score at randomization was 2.73 (3.37); and there were no changes from baseline or differences between treatments in MADRS scores after randomization. FAST total scores improved during the oral aripiprazole and AOM 400 stabilization phases. This improvement was maintained in patients receiving AOM 400, while scores deteriorated in patients receiving placebo ( $p = 0.0287$  at last visit). Brief QoL.BD scores were unchanged throughout the study with no differences between treatments.

Conclusions: Patients with BP-I experiencing a manic episode showed symptomatic and functional improvement during stabilization on oral aripiprazole and AOM 400. Improvements were maintained over 52 weeks for patients continued on AOM 400 treatment, but not for those switched to placebo. Depressive symptoms were not exacerbated.

#### **T15. SAFETY OF LURASIDONE IN ADOLESCENTS WITH SCHIZOPHRENIA: INTERIM ANALYSIS OF A 24-MONTH, OPEN-LABEL EXTENSION STUDY**

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**Abstract:** Objective: Use of second-generation antipsychotics (SGA) in the treatment of adolescents with schizophrenia has been associated with different safety concerns, including weight gain, increased glucose and lipids, and hyperprolactinemia. (1, 2) However, limited data are available from prospective studies that demonstrate the long-term safety of SGA in this population. Lurasidone is an atypical antipsychotic that has demonstrated efficacy in the treatment of schizophrenia in both adults and adolescents. The aim of the current open-label trial was to examine the long-term safety of lurasidone in adolescents with schizophrenia.

Methods: Patients aged 13-17 years old with a DSM-IV-TR diagnosis of schizophrenia who completed a 6-week, double-blind, placebo-controlled lurasidone treatment study were eligible for enrolment in an extension study of the safety and effectiveness of 24 months of open-label, flexible-dose treatment with lurasidone 20-80 mg/d. This analysis summarizes the safety results from an interim analysis of an ongoing 2-year study. Safety measures included frequency of treatment emergent adverse events, and changes in mean weight (vs. expected weight, based on CDC growth charts), median fasting and non-fasting metabolic parameters, and median prolactin levels (observed case analysis).

Results: A total 180 patients entered the extension study (male, 57.8%; mean age, 15.5 years), of whom 72.2% and 37.8% of patients completed clinic visits at the interim time points Week 28 and 52, respectively. A total of 38.3% discontinued before 52 Weeks. Reasons for study discontinuation consisted of withdrawal of consent (12.8%), adverse events (11.1%), lost to follow-up (4.4%), lack of efficacy (4.4%), and other reasons (5.6%). The mean daily dose of lurasidone during the open-label treatment period was 55.8 mg/d, and the proportion of patients using a modal dose of 20 mg, 40 mg, 60 mg, and 80 mg was 2.3%, 40.4%, 25.1%, and 32.2%, respectively. Discontinuation due to adverse events occurred in 11.1% of patients; the 3 most frequent adverse events leading to study discontinuation were schizophrenia (3.9%), suicidal ideation (1.7%), and psychotic disorder (1.1%). In the placebo-to-lurasidone treatment group (N=57), the 5 most frequent adverse events were headache (24.6%), nausea (14.0%), increased weight (14.0%), anxiety (10.5%), and agitation (10.5%); and in the lurasidone-continuation group (N=123), the 5 most frequent adverse events were headache (16.3%), anxiety (11.4%), agitation (10.6%), schizophrenia (8.9%), and depression (8.1%). Small median changes at 12 months, relative to open-label baseline, were noted for cholesterol (+0.7 mg/dL), triglycerides (+4.1 mg/dL), glucose (+0.6 mg/dL), and prolactin (males, +0.1 ng/mL; females, +0.5 ng/mL). Mean change in weight at 12 months, relative to double-blind baseline, was +5.7 kg (vs. an expected weight gain of +2.8 kg).

Conclusion: Long-term treatment with lurasidone was associated with few effects on body weight, lipids, glucose, and prolactin in this interim analysis of 12-month data from an open-label 24-month study of adolescents with a diagnosis of schizophrenia. The safety profile was consistent with results from previous adult studies with lurasidone.

Sponsored by Sunovion Pharmaceuticals, Inc.

ClinicalTrials.gov identifier: NCT01914393

## **T16. EFFECTIVENESS OF LURASIDONE IN ADOLESCENTS WITH SCHIZOPHRENIA: INTERIM ANALYSIS OF A 24-MONTH, OPEN-LABEL EXTENSION STUDY**

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**Abstract:** Objective: Approximately one-third of cases of schizophrenia have an onset before the age of 20, however, efficacy data from prospective studies are still relatively limited, especially data from studies of 12 months or longer (1). Lurasidone is an atypical antipsychotic that has demonstrated efficacy in the treatment of schizophrenia in both adults and adolescents. The aim of the current open-label trial was to obtain preliminary data on the long-term effectiveness of lurasidone in adolescents with schizophrenia.

Methods: Patients aged 13-17 years old with a DSM-IV-TR diagnosis of schizophrenia who completed a 6-week, double-blind, placebo-controlled lurasidone treatment study were eligible for enrolment in an extension study of the safety and effectiveness of 24 months of open-label, flexible-dose treatment with lurasidone 20-80 mg/day, with an initial dose of 40 mg/d for the first 7 days. This analysis summarizes the effectiveness results from an interim analysis of an ongoing 2-year study. Effectiveness measures included the Positive and Negative Syndrome Scale (PANSS) total and positive and negative subscale scores, and the Clinical Global Impression-Severity (CGI-S) score.

Results: A total of 180 patients entered the extension study (male, 57.8%; mean age, 15.5 years); 72.2% and 37.8% patients completed a clinic assessment at the interim time points Weeks 28 and 52, respectively. The mean daily dose of lurasidone during the open-label treatment period was 55.8 mg/d, and the proportion of patients with a modal dose of 20 mg, 40 mg, 60 mg, and 80 mg was 2.3%, 40.4%, 25.1%, and 32.2%, respectively. At the end of 6 weeks of double-blind treatment, improvement was greater with lurasidone (N=123) compared with placebo (N=57) on the PANSS total score (-21.3 vs. -14.9), PANSS positive subscale score (-7.0 vs. -4.1), PANSS negative subscale score (-4.9 vs. -3.7), and CGI-S score (-1.0 vs. -0.6). After 28 weeks of open-label treatment with lurasidone, additional improvement (from open-label baseline) was observed on the PANSS total score (-7.9), PANSS positive subscale score (-2.9), PANSS negative subscale score (-1.6), and CGI-S score (-0.6). Patients initially treated with double-blind placebo demonstrated greater improvement during the open-label lurasidone treatment phase, resulting in a level of improvement in PANSS total and subscale scores at week 28 that was similar to the improvement observed in the lurasidone continuation treatment group. Reasons for study discontinuation consisted of withdrawal of consent (12.8%), adverse events (11.1%), lost to follow-up (4.4%), lack of efficacy (4.4%), and other reasons (5.6%).

Conclusion: Long-term treatment with lurasidone was associated with sustained improvement in psychotic symptoms as measured by the PANSS total and subscale scores this interim analysis of 28 weeks month data from an open-label 24-month extension study of adolescents with a diagnosis of schizophrenia.

Sponsored by Sunovion Pharmaceuticals, Inc.

ClinicalTrials.gov identifier: NCT01914393

#### **T17. SINGLE AND MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND CARDIAC SAFETY OF EXTENDED-RELEASE VILOXAZINE (SPN-812 ER) IN HEALTHY ADULT SUBJECTS**



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**Abstract:** Introduction: A novel, once-daily, non-stimulant attention-deficit/hyperactivity disorder (ADHD) treatment, extended-release (ER) viloxazine (SPN-812 ER) is in development. Stimulants such as methylphenidate are the first-line pharmacotherapy for ADHD. However, some ADHD patients cannot take stimulants due to adverse effects or contraindications. Non-stimulants provide an invaluable therapeutic alternative. SPN-812 ER is a structurally distinct, bicyclic norepinephrine reuptake inhibitor, with antagonistic activity observed at 5-HT<sub>7</sub> and 5-HT<sub>1B</sub> receptors and agonistic activity at 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors. Viloxazine, previously approved as an antidepressant in the EU, has had a comprehensive review of its pharmacological, clinical, and safety profiles, which revealed no major safety concerns. The objectives of the present study were to determine the safety, tolerability, and cardiac effects of single ascending doses and multiple ascending doses of SPN-812 ER in healthy adult subjects.

Methods: This was a single-center, randomized, double-blind, placebo-controlled study. Volunteers were healthy adults, 18-45 years old, non-smokers, with a body mass index of 18–28 kg/m<sup>2</sup>. Eight subjects in each of 7 dose cohorts were randomized in a 3:1 ratio to receive a specified dose of active treatment (SPN-812 ER 300 mg, 600 mg, 900 mg, 1200 mg, 1500 mg, 1800 mg, or 2100 mg) or placebo. Cohorts 1-3 were conducted in parallel. Cohorts 4-7 were dosed sequentially given that the tolerability of the previous dose was demonstrated. Subjects were administered a single dose on Day 1 followed by a 48-hour washout period, then were dosed once daily for 5 consecutive days (Days 3-7: multiple dose phase). Adverse events (AEs) and electrocardiograms (ECGs) were recorded throughout the study.

Results: The safety population included 56 subjects. Baseline characteristics were similar across groups. Twenty-three (41.1%) subjects reported at least one TEAE and 19 (33.9%) subjects reported at least one treatment-related AE determined by the investigator. No serious AEs or deaths were reported. Two subjects (3.6%) during the multiple dosing phase at 2100 mg SPN-812 ER, discontinued due to AEs, vomiting and costochondritis, respectively. The most common TEAEs overall were headache (10 subjects, 17.9%), and dizziness and nausea (6 subjects each, 10.7%). Headache, dizziness, and nausea were also the most common treatment-related AEs. During the single-dose phase, headache, somnolence, and dizziness (3, 4, and 3 subjects, respectively) were the most common AEs; of these 10 subjects, more than half occurred in the two highest dose groups. In the multiple-dose phase, the most common TEAEs were headache, nausea, dizziness and vomiting (6, 4, 3, and 3 subjects, respectively); all the nausea and vomiting and half the headaches occurred in the highest dose group. The majority of TEAEs in both phases were mild. The cardiac concentration-effect modeling data (e.g., placebo-adjusted, baseline-corrected QT interval based on the Fridericia correction method [QTcF]) showed no significant effect of SPN-812 ER on cardiac repolarization or ECG parameters (demonstrated by the significant negative slope,  $p=0.0091$ ) other than a slight increase in heart rate consistent with the known anticholinergic effect of viloxazine.

Conclusions: SPN-812 ER was safe and well tolerated from 300 to 2100 mg/day as a single dose, and from 300 to 1800 mg/day as multiple doses given once daily for 5 consecutive days.

## **T18. THE PROMINENT ROLE OF CLINICAL PHARMACOLOGY AND DOSING IN PMAS OF APPROVED NMES IN THE LAST TEN YEARS**

**Abstract:** Introduction: Since the passage of the Prescription Drug User Fee Act (PDUFA) in 1992, there has been a significant expediting of the drug approval process. From 1992 to 2012, the average time to market for drugs has decreased from 2 years to 1.1 years. Post marketing agreements (PMAs) are an important tool utilized by the FDA to ensure drug safety and have also allowed for dose optimization of drugs. With the current PDUFA V cycle placing emphasis on enhanced communication with Sponsors during drug development, a review of PMAs in PDUFA IV (2007-2011) and PDUFA V (2012-2017) was undertaken with year 2012 as the inflection point. Furthermore, this research also evaluated the types of PMAs that the agency is requiring.

Using the DARRTS database, NME's (n=196) approved from 2006-2015 were evaluated. Accelerated approval, imaging devices, and enzyme replacement therapies were excluded as they are not representative of the typical drug approval process. Drug approval letters were reviewed and all post marketing agreements (n=473) were noted. Post Marketing Agreements were then classified under 7 categories based on prevalence (e.g., efficacy, clinical pharmacology, safety).

A significant portion of the PMAs required over the past 10 years were clinical pharmacology (CP) issue related (n=176, 37%), and a great majority in this CP group were dosing related (n=151 or 32 % of the total PMAs). These dosing issues were further subcategorized into -

- A- Disease state dosing - renal impairment, hepatic impairment studies
- B-Metabolism dosing- CYP induction or inhibition
- C-Concomitant use dosing- Drug drug interaction studies
- D-Dose-response – dose related safety/efficacy studies

Results: Overall: Between 2006-2015 about one-third of the NME PMAs required were dosing related. Further, in these dose-related PMAs (n=151), metabolism (n=52; 34 %; B) was the most frequently evaluated followed by disease state (n=46; 30%; A), concomitant use (n=37; 25%; C) and dose response (n=16; 11%; D).

PDUFA V versus PDUFA IV: In PDUFA IV cycle, a total of 77 NMEs were approved (15.4 NMEs/year) which amongst them had 250 PMAs (3.3 PMAs/NME). In the current PDUFA V cycle, a total of 106 NMEs have been approved in 4 years (26.5 NMEs/year) with 186 PMAs (1.8 PMAs/NME). There was a statistically significant increase in the number of NME's approved in the PDUFA V cycle versus PDUFA IV (p=0.0043), and there was a statistically significant decrease in PMA's/NME (p=0.0265) indicating that PDUFA V cycle drugs have required less post marketing studies in comparison to the previous PDUFA IV cycle.

Our survey of PMAs has shown that in the drug approval process PDUFA V has indeed improved communication with sponsors. However, more progress needs to be made from a dose optimization standpoint and both the Agency and Sponsors need to focus on and identify areas for improvement here. The resolution moving forward is direct and early IND communication with Sponsors, and the timely convey of OCP viewpoints related to dosing. This should be both practical and feasible with the addition of the project management team in OCP.

## **T19. A CLINICALLY USEFUL SCREEN FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN ADULT PSYCHIATRIC OUTPATIENTS**

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**Abstract:** Background: Attention deficit hyperactivity disorder (ADHD) is a serious illness that is frequently underdiagnosed in adults. The goal of the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project was to determine if it was possible to identify 1 or 2 ADHD criteria that could serve as “gate” criteria to screen for the disorder.

Methods: One thousand one hundred and thirty-four psychiatric outpatients were evaluated with a semi-structured diagnostic interview for DSM-IV ADHD. We computed the sensitivity, specificity, positive and negative predictive values of each of the 18 ADHD criteria to identify the 1 or 2 ADHD criteria that could be used to screen for the disorder. We conducted a validation and cross-validation analysis by splitting the sample in half.

Results: In both the validation and cross-validation samples a 2-item screen of difficulty sustaining attention and fidgetiness had a sensitivity greater than 90%. The negative predictive value of the 2-item screen was greater than 95%.

Conclusions: Clinicians can screen for adult ADHD by inquiring about 2 features of the disorder (i.e., difficulty sustaining attention and fidgetiness) the presence of which captures most patients with the disorder and the absence of which rules out the disorder.

## **T20. SERVING THE NEEDS OF OUR DIVERSE POPULATION: IT ALL BEGINS WITH RECRUITMENT!**

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**Abstract:** Background/Introduction: At the 35th Annual (1995) NCDEU Conference we presented information on “Increasing Ethnic Diversity and Research Patient Recruitment in the Nineties...,” reflecting trends of dramatic increases in both the Hispanic and Asian proportions of our Southern California population. In tandem, there was also a trend of a slight decrease in the Black/African-American percentage and an almost 50% reduction in the proportionate White/Caucasian population. Now, more than twenty years later, our diversity has been even further enhanced. To better serve the needs of our increasingly diverse population, recruitment techniques have become more diversified, segmented and geo-targeted as well.

Methods: To compare our 1975-to-1995 recruitment tools, techniques and successes, which were almost totally reliant on newspapers, radio and television, with more recently implemented patient/subject recruitment-related efforts, we compiled data on the last 361 subjects enrolled into a trial at Pharmacology Research Institute (PRI), including early 2017. We limited the indications to Binge Eating Disorder, Migraine Headache and Smoking Cessation. We looked at both Race: American Indian/Alaskan Native, Asian, Black/African-American, Hawaiian/Pacific Islander, White/Caucasian and Other/Mixed, and Ethnicity: Hispanic and Non-Hispanic. We will primarily share data on race. We analyzed race-related data from three conceptual lenses: 1. Traditional versus non-traditional recruitment methods, i.e., Internet-based and database-related recruitment strategies; 2. Recruitment resources'

relative/comparative effectiveness in attracting individuals from each racial category; and, 3. Screen failure and completion rates by racial category.

Results: From smart-phones to mobilized websites with study-specific landing pages, Internet-based recruitment strategies have now surpassed (although not totally supplanted) traditional recruitment avenues, such as newspapers, radio and television. Indeed 58% of our adult enrollees (ages 18-to-65) were recruited via the Internet and 22% vis-à-vis traditional advertising. An additional 20% were successfully enrolled via our patient database, consisting of both prior study participants and respondents who either did not fulfill prior study protocol criteria or were screen failed for reasons other than non-compliance. Only one American Indian/Alaskan Native was successfully recruited, via the Internet; 33% of Hawaiian/Pacific Islanders, 51% of Black/African-Americans, 58% of Asians and 59% of White/Caucasian subjects were recruited via the Internet (including some central ad campaigns). As for traditional advertising methods, 67% of Hawaiian/Pacific Islanders, 26% of Black/African-Americans, 25% of Asians and 21% of White/Caucasians were recruited via newspapers, radio or television ads. Screen failure rates were lowest amongst Hawaiian/Pacific Islanders (0%) and Black/African-Americans (18.7%). Completion rates were highest amongst Hawaiian/Pacific Islanders (100%) and White/Caucasians (88.9%).

Conclusions:

- The Internet has unquestionably facilitated our ability to better reach and serve our more diverse population.
- The ability to geo-target reasonably close, ethnically diverse, communities has cost- and logistical-advantages over traditional recruitment tools, especially television and radio.
- Traditional recruitment techniques have been supplemented and not, yet, completely supplanted by Internet-based strategies.
- Intuitively, we believe, when it comes to serving the needs of our diverse population, having an ethnically and racially diverse research team is advantageous as well.

## **T21. H2 ANTAGONISTS AS POTENTIAL BIOMARKERS OF ADHERENCE IN CLINICAL RESEARCH: DETECTION WINDOWS IN URINE**

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**Abstract:** Objective: Adherence with study drugs in clinical trials is critical for determination of efficacy of pharmacological interventions. Urinary measurements of drug and metabolites have been attracted significant interest due to simplicity, high subject acceptance, safety and cost. We investigated the urinary levels of over the counter H2 antagonists (ranitidine, nizatidine and famotidine) as objective markers of adherence in clinical trials.

Method: Eight healthy subjects not taking H2 antagonists were administered ranitidine 15 mg/day for 2 days, nizatidine 30 mg/day for 3 days and famotidine 8 mg/day for 2 days consecutively. Supervised urine samples were collected each day for 14 days. Detection of urinary ranitidine, nizatidine, famotidine and metabolites was performed using High Performance Liquid Chromatography with Mass Spectrometry (LC-MS). Detection range was set between 0.5-2000 ng/ml.

Results: Ranitidine was detected in urinary samples from 24 hours ( $307.93 \pm 326.07$  mg/ml) to 144 hrs ( $2.01 \pm 2.07$  ng/ml) after the last dose. Nizatidine was detected in urine samples from 24 hours ( $117.81 \pm 112.83$  ng/ml) to 48 hours ( $16.91 \pm 21.66$  ng/ml) after last dose. Famotidine was detected in urine samples from 24 hours ( $332.08 \pm 389.22$  ng/ml) to 72 hours ( $12.83 \pm 14.24$  ng/ml) after last dose. There were no side effects reported ingestion of H2 antagonists. Conclusion: Adherence with study drugs can be measured objectively and in real time by incorporating low doses of ranitidine, nizatidine and famotidine in study drugs. Ranitidine has a 6-day detection window, nizatidine has a 2- day detection window and famotidine has a 3-day detection window.

## **T22. A PILOT STUDY OF SD-809 (DEUTETRABENAZINE) IN TICS ASSOCIATED WITH TOURETTE SYNDROME**

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**Abstract:** Objective: This study explored the safety, tolerability and preliminary efficacy of SD-809 (deutetrabenazine) in adolescents with moderate to severe tics associated with Tourette syndrome (TS).

Background: SD-809, an inhibitor of vesicular monoamine transporter type 2 (VMAT2), depletes presynaptic dopamine and therefore has utility in the treatment of various hyperkinetic movement disorders including tics.

Methods: In this open-label study, 12-18-year-old patients with TS-related troublesome tics were titrated up to 36 mg/day over 6 weeks to adequately control tics while maintaining tolerability, followed by maintenance at this dose for 2 weeks. An independent blinded rater assessed tic severity using the Yale Global Tic Severity Scale (YGTSS) and tic impact using the TS-Clinical Global Impression (TS-CGI). Other secondary outcome measures included Patient Global Impression of Change (PGIC). Safety was assessed by monitoring adverse events (AEs), vital signs, physical examination, 12-lead ECGs, clinical laboratory tests and safety scales.

Results: Twenty-three (23) enrolled patients received SD-809 and had at least 1 post-baseline YGTSS assessment. Mean (SD) YGTSS Total Tic Score at baseline was 31.6 (7.9) which improved by 11.6 (8.2) at endpoint, representing a 37.6% reduction in tic severity ( $p < 0.0001$ ). At week 8, the mean (SD) TS-CGI score improved by 1.2 (0.81) points ( $p < 0.0001$ ). PGIC results at week 8 indicated that 75% of subjects described themselves as much or very much improved compared to before treatment. Mean dose at endpoint was 32.1 mg/day. One week after withdrawal of SD-809, statistically significant increases were observed in a number of YGTSS component scores. No serious or severe AEs were reported. One subject withdrew from the study for an AE of irritability that was unrelated to study drug.

Conclusions: SD-809 was well tolerated and associated with clinically meaningful improvement in tic severity. Our findings support further development of SD-809 for treatment of TS.

## **T23. THE NOCEBO PHENOMENON IN A SERIES OF FIRST-TIME-IN-HUMAN, DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE ASCENDING-DOSE TRIALS OF CNS ACTIVE AGENTS**

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**Abstract:** The Nocebo Phenomenon in a Series of First-time-In-Human, Double-Blind, Placebo-Controlled, Single Ascending-Dose Trials of CNS Active Agents.

Background: Subjects receiving placebo (PBO) in double-blind trials often report AEs similar to those reported by subjects receiving study drug. This phenomenon, opposite that of the PBO effect, is known as the ‘nocebo’ (NBO) effect. While poorly understood, it is believed to be driven in part by negative expectancy, i.e., attributed to the communication of potential AEs to prospective study participants. Factors contributing to the NBO effect in Phase I healthy volunteer (HV) studies are particularly not well-characterized.

Objective: To characterize the NBO effect in a series of first-time-in-human (FTIH) single ascending-dose (SAD), double-blind, PBO-controlled studies of investigational neurotherapeutic agents.

Methods: PBO group (total N=80) AE data were pooled from 5 separate FTIH HV studies. Prior to analysis, all PBO subjects were prospectively categorized as having received PBO in a low (LD) or high (HD) dose cohort, based on the SAD regimen utilized. The study drugs evaluated included a GALR-3 antagonist, a MAO-B inhibitor, and 3 PDE inhibitors. Specific hypotheses tested were that:

- 1) Overall AE incidence would not differ between PBO and drug
- 2) % of AEs rated as moderate or severe (MOD/SEV) would not differ between PBO and drug
- 3) % of AEs considered Related/Possibly Related (REL/PR) to study drug would not differ between PBO and drug
- 4) AE incidence would not differ between subjects receiving PBO in HD vs LD cohorts
- 5) % of PBO AEs assessed as REL/PR to study drug would not differ between HD vs LD cohorts
- 6) PBO AE incidence would not differ between female vs male subjects, nor between elderly vs non-elderly subjects

Statistical significance was assessed by Chi-square or t-test (two-tailed) where appropriate. A p-value of  $\leq 0.05$  was regarded as significant.

Results: Overall AE incidence for PBO (23/80, 28.8%) did not differ from that for study drug (64/227, 28.2%). Similarly, neither the proportion of AEs rated as MOD/SEV (9.6% vs 12.1%, respectively;  $p=0.64$ ), nor the proportion of AEs considered REL/PR to study drug (63.5% vs 67.2%, respectively;  $p=0.63$ ), differed between PBO vs study drug. While a few AEs occurred at greater frequency in the drug group (e.g., vomiting, 4.0% vs 1.25% for drug vs PBO, respectively), the 2 most common PBO AEs (headache [7.5%]; dizziness [6.3%]) were the same as the 2 most common AEs in the pooled drug group (headache [4.8%]; dizziness [7.0%]). AE incidence in female PBO subjects was twice that in male PBO subjects (38.9% vs 20.5%;  $p=0.07$ ). AE incidence in elderly PBO subjects (40%) was greater than in non-elderly PBO subjects (25%), but not significantly so ( $p=0.199$ ). PBO AE incidence did not differ between HD and LD cohorts (33.3% vs 24.4%, respectively,  $p=0.377$ ); however, a significantly greater

proportion of PBO AEs in HD cohorts were blindly rated by the Principal Investigator (PI) as REL/PR to study drug than were the PBO AEs in LD cohorts (81.8% vs 26.3%;  $p<0.001$ ). Conclusion: The NBO effect may be significant in FTIH SAD HV studies and is likely driven by both subject as well as PI expectations. Such effects can theoretically occur in any treatment group (i.e., AEs in the drug group can also occur via a NBO effect) thereby impairing early evaluation of investigational drugs, even delaying/preventing further development. Although not evaluated in this analysis, NBO effects in Phase I multiple ascending dose (MAD) HV studies may be particularly problematic because they could result in lower adherence/higher dropout rates.

## **T24. TOLERABILITY AND EFFICIENCY OF DESVENLAFAXINE IN METHADONE MAINTAINED PATIENTS SUFFERING FROM MAJOR DEPRESSIVE DISORDER**

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**Abstract:** Background: Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders among opioid-dependent individuals. Comorbid depression confers poor outcome, including high risk of continued drug abuse and a high relapse rate. Clinical-trial findings in patients undergoing Methadone Maintenance Therapy (MMT) have been negative for selective serotonin reuptake inhibitors (SSRIs) while tricyclic antidepressants (TCAs) produced mixed results despite potential for cardiotoxicity. Desvenlafaxine (DESV) is an antidepressant which works through a dual mechanism by acting as a serotonin and norepinephrine reuptake inhibitor (SNRI) and has low potential for cardiotoxicity. The main objective of this study is to assess the tolerability and efficacy of DESV in MDD patients on MMT.

Methods: Eighteen opioid users on MMT and diagnosed with MDD as asserted by a psychiatrist, received DESV (50-100 mg/day) for 8 weeks and were followed at week- 0, 2, 4, 6 and 8 as to: 1) Depressive symptoms using Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAM-D17) and Clinical Global Improvement (CGI); 2) Safety and tolerability of DESV using the Systematic Assessment for Treatment Emergent Events General Inquiry (SAFTEE-GI) and an EKG to monitor QTc interval.

Results: Compared to baseline (week-0), DESV significantly decreased MADRS ( $P<0.001$ ), HAM-D17 ( $P<0.001$ ) and CGI ( $P<0.001$ ) scores at week-8. In addition, percentage of responders and remitters on MADRS at week-8 was 61 % and 50 % respectively. Importantly, all patients had a normal QTc measurement with no significant impairment at week 8.

Conclusion: DESV was well tolerated and had no impact on QTc. This medication was associated with response and remission rates comparable to those found in the general depressed population without opioid use disorder. Thus, DESV may be a promising contender for clinicians and deserves further exploration in large double-blinded clinical trials.

## **T25. DATA SURVEILLANCE TO IMPROVE ENDPOINT ASSESSMENT IN GLOBAL ALZHEIMER'S DISEASE**

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**Abstract:** The development of effective drugs in Alzheimer's disease has been challenging. Recently, several promising drugs have failed to show efficacy. Measurements at baseline and during the study to assess the efficacy of the drug depend on consistent, standard administration of scoring instruments. However, when the interviews and assessments of subjects during a clinical study are independently monitored, administration and scoring errors by the persons performing the assessments (the "raters") are frequently detected. In a large, global clinical trial, 13,440 ADAS-Cogs and MMSE from 5 study visits were reviewed for administration and scoring errors by doctoral-level clinicians for scoring and administrative accuracy. Forty-three percent of the visits were found to have at least one administrative or scoring error in the application of the measurement instrument. Thirty-five percent of the errors that were detected were scoring errors that led to a recommended scoring change. Scoring errors impacted eligibility conclusions in <3% of the screening visits with errors had subjects being approved for inclusion or potentially excluded based on erroneously scored and administered Mini-Mental Status Exams (MMSE). If efficacy in a clinical trial is defined as a 3-point change in the ADAS-Cog, identifying 35% of scoring errors which led to a recommended scoring change will drastically improve the quality of the data. Data Surveillance was effective at identifying administration and scoring errors, retraining raters and correcting erroneous scores resulting in improved data quality and confirmed eligibility of subjects. Future training programs should be informed by the lessons learned on most frequently occurring scoring and administrative errors.

## **T26. TRANSLATION OF THE ZARIT BURDEN INTERVIEW 22 ITEMS (ZBI-22) INTO 95 LANGUAGES: CHALLENGES AND IMPORTANCE OF THE CONCEPTUAL DEFINITION OF THE ORIGINAL VERSION**

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**Abstract:** Objectives. The Zarit Burden Interview (ZBI) is a caregiver self-report measure, developed in US English, specially designed to reflect the stresses experienced by caregivers of dementia patients. Caregivers are asked to respond to a series of 22 questions about the impact of the patient's disabilities on their life. For each item, caregivers are invited to indicate how often they felt that way (never, rarely, sometimes, quite frequently, or nearly always). The objectives of this study were to present the challenges of the translation of the ZBI-22 into 95 languages and the importance of developing a conceptual definition for each item.

Methods. In most languages, the standard translation process consisted of: 1) Conceptual definition of each item developed in collaboration with the developer 2) Forward/backward translation step including a review of the back-translation by Prof. Zarit; 3) Clinician review; and 4) Cognitive interviews with five caregivers.

Results. No cultural issues were identified during the process. Most of the issues were semantic. One of the greatest challenges was in finding the most appropriate words for the description of the feelings of the caregivers (i.e., do you feel stressed, embarrassed, angry, uncomfortable, afraid); each word representing a specific concept needing a clear differentiation. The



conceptual definition by Prof. Zarit was essential to help the translation teams in finding the most appropriate word in each language. Items 7 and 13 raised queries given their idiomatic nature (7. Are you afraid of what the future holds for your relative?; 13. Do you feel uncomfortable about having friends over?). The interventions of Prof. Zarit helped the teams in finding appropriate translations. Examples of solutions found are presented.

Conclusion. The input of the developer in providing conceptual definitions and clarifications during the process was essential in developing translations of the ZBI-22 conceptually equivalent to the original.

## **T27. THE RESIDUAL SYMPTOMS AND FUNCTIONING OF MAJOR DEPRESSIVE PATIENTS AFTER PARTIAL RESPONSE TO ACUTE ANTIDEPRESSANT TREATMENT IN CLINICAL SETTING**

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**Abstract:** Background: Little is known about presence of residual symptoms and their specific contribution on functioning that occur in representative patients after antidepressants treatment in routine clinical practice. This study describes the types and frequency of residual symptoms and their relationship to functioning after remission or partially responding to acute 8-12 week antidepressants treatment.

Methods: This study is a cross-sectional, multi-site, non-interventional design. 1503 outpatients with major depressive disorder (MDD) were included within the context of partially responding to 8-12 weeks treatment. We assessed residual symptoms and multiple domains of psychosocial functioning and quality of life using self-report measures. We also analyzed the factors associated with psychosocial functioning of this sample.

Results: Among responders, 51.2% of MDD patients (770/1503) achieved remission and 10% of remitters were free of any core residual symptoms. Core residual symptoms of remitters were sleep disturbance (66.6%), fatigability (32.3%), concentration difficulty (31.3%), appetite/weight disturbance (28.8%), altered psychomotor (23.2%), sadness (21.9%), loss of interest (21.2%). Mild somatic symptoms presented after remission were headache (31.9%), intestinal problem (31.3%), heart pounding/racing (26.4%), gastric discomfort (22.3%), dizziness (22.2%) and stomachache (20.6). Remitters had better occupational, social, family functioning and better quality of life and satisfaction than non-remitters. Residual fatigue (odds ratio [OR] 1.56-2.45), altered psychomotor (OR 1.38-1.88), sleep disturbance (OR 1.21-1.32) and appetite/weight disturbance (OR 1.22-1.29) contributed to the impairment of all three dimensions of functionality.

Conclusions: Residual symptoms are prevalent in MDD patients after remission or response, and our findings contribute to understand better the role of specific residual symptoms on functional impairment. To achieve normal functioning, intervention on specific residual symptoms needs to be focused.

## **T28. ANTIDEPRESSANT AUGMENTATION AND CO-INITIATION TREATMENT IN ACUTE MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW, META-ANALYSIS AND METAREGRESSION ANALYSIS**

*Britta Gallings\*, Christoph Correll*

**Abstract:** Introduction: Despite pharmacological advances, management options for patients with major depressive disorder (MDD) remain suboptimal. Being common and commonly only suboptimally controlled, MDD is the leading cause for disability worldwide [1].

Recommendations after non-response include AD dose optimization, switch to another AD, switch to or augmentation with psychotropic agents from other classes with AD properties, or the augmentation with a second AD.

AD co-treatment is frequent in clinical practice, mostly being employed as augmentation rather than co-initiation of two agents from the beginning of treatment. However, evidence for the efficacy and tolerability of both AD co-treatment strategies is slim.

Most AD co-treatment trials in MDD have studied co-initiation rather than augmentation. Moreover, the only previous meta-analysis of antidepressant co-treatment, finding efficacy advantages of AD+AD co-treatments compared to monotherapy regarding remission (relative risk=2.71, 95%CI=1.69-4.35) and response (relative risk=1.5, 95%CI=1.21-1.97) [2], was restricted to co-initiation studies, not representing clinical practice.

In view of the prevalence of AD+AD treatment and the paucity of evidence in its support, we conducted a comprehensive meta-analysis of the efficacy and safety of i) AD augmentation and ii) AD co-initiation compared to AD monotherapy in patients with MDD.

Methods: Systematic search from database inception through January 26, 2016 for randomized controlled trials comparing co-treatment with a second AD to AD monotherapy in MDD. Random-effects meta-analyses for co-primary outcomes (overall symptom reduction, study-defined response) and secondary outcomes (all-cause and specific-cause discontinuation, partial response, remission, adverse effects). All analyses were conducted separately for augmentation and co-initiation studies and for high-quality (double-blind and intent-to-treat data) and low-quality studies (open label and/or observed cases).

Results: Meta-analyzing 45 studies (comparisons (N)=58, n=4238, duration=6.7±1.9 weeks), no difference emerged for AD augmentation (N=8, n=1216, duration=5.9±2.9 weeks) compared to monotherapy regarding overall symptom reduction (N=7, n=822, SMD=-0.23, 95%CI=-0.60-0.14, p=0.224) or response (N=6, n=1033, RR=1.08, 95%CI=0.87-1.33, p=0.499). Conversely, AD co-initiation (studies=37, N=50, n=3022, duration=6.9±1.6 weeks) was superior for both symptom reduction (N=46, n=2713, SMD=-0.93, 95%CI=-1.20, -0.66, p<0.001) and response (N=33, n=1,996, RR=1.29, 95%CI=1.22-1.37, p<0.001). However, while overall effect sizes were large, they were only small in “high-quality” studies for symptom reduction (N=16, n=715, SMD=-0.304, 95%CI=-0.566 to -0.042, p=0.023) and treatment response (N=11, n=430, RR=1.22, 95%CI=1.09-1.38 p=0.001).

No between-group differences emerged regarding all-cause, inefficacy-related or adverse effect (AE)-related discontinuation in either augmentation or co-initiation studies. The AE burden was significantly higher in 3/9 outcomes (33.3%) reported in ≥2 augmentation studies (≥1AE: p<0.001; dry mouth: p=0.006, weight gain ≥7%: p=0.010), and in 1/21 outcomes (4.8%) reported in ≥2 co-initiation studies (hypersomnia: p=0.041). In high-quality co-initiation studies, tremor (p=0.047) and sweating (p=0.006) emerged more often with co-initiation.

Conclusion: In short-term studies, AD augmentation after partial or full non-response lacks evidences for superior efficacy, whereas AD+AD co-initiation seems to potentially increase or speed up depressive symptom reduction and response, with relatively little additional AE burden.

## **T29. PREVALENCE OF SUBTHERAPEUTIC PRESCRIBING OF ANTIDEPRESSANTS IN THE UNITED STATES**

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*inVentiv Health*

**Abstract:** Introduction: There is evidence of the use of subtherapeutic doses of antidepressants for the treatment of depression (1,2). Purported reasons for subtherapeutic prescribing may be related to over-cautiousness by general practitioners (GPs), adherence to the “start low and go slow” approach, efforts to build tolerance and minimize adverse effects, or lack of evidence of dosing effects with many antidepressants. However, there is concern that this practice is leading to suboptimal treatment and poor patient outcomes (1). To assess how common subtherapeutic prescribing for depression is in the United States (US), this research investigated the prescribing practices of office-based physicians for patients with major depressive disorder (MDD) prescribed SSRIs and SNRIs.

Methods: Data were obtained from the TreatmentAnswers™ database. TreatmentAnswers is a monthly survey of 3,219 US office-based physicians, covering 30 specialties. One day each month, participating physicians complete a survey about patient activity during that work day. Information collected includes visit information, patient/physician demographics, diagnostic information, and intended drug therapy. Data collected are projected to the wider US population using a standardized projection factor. This investigation included a review of the 2015 intended prescription data for patients with a reported ICD-9 diagnosis of MDD (single episode or recurrent) who were prescribed a brand-name SSRI or SNRI as reported by their physician. Data were summarized to show the frequency for which various doses of SSRIs/SNRIs were prescribed, as well as dosing practices by physician specialty (psychiatrist versus general practitioner). Daily doses prescribed were categorized as therapeutic or subtherapeutic (below the minimum daily dose for adults with MDD, as specified on the FDA label).

Results: In 2015, Lexapro (22%) and Zoloft (22%) were the most frequently prescribed SSRIs for MDD; Cymbalta (38%) was the most frequently prescribed SNRI. Across all prescribed brand-name SSRIs and SNRIs, 79% of intended daily prescription doses were classified as therapeutic, 9% as subtherapeutic, 2% as exceeding the dosing guidelines, and 10% not able to be categorized (e.g., physician did not report dose). Cymbalta and Fetzima were the most likely to be prescribed at subtherapeutic daily doses. When broken out by physician specialty, GPs prescribed subtherapeutic doses of SSRIs/SNRIs at a slightly greater frequency (12%) than psychiatrists (8%) and did not tend to prescribe doses exceeding the dosing recommendations. Conclusions: Overall, US physicians generally prescribe therapeutic doses of SSRIs and SNRIs for MDD, although there is some evidence of subtherapeutic dosing, which is slightly more common with certain medications and among GPs than psychiatrists. Future research should evaluate the reasons for, timing and impact of subtherapeutic dosing. It may be, for example, that subtherapeutic dosing is temporarily employed as a starting dose until a therapeutic dose is achieved. A longitudinal evaluation of dosing and outcome would be beneficial. Additionally, this research used physician-reported data, which may be limited by self-report and not reflect actual patient use.

## **T30. MECHANISMS OF PAIN AND OPIOID INDUCED HYPERALGESIA**

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**Abstract:** Opioid-induced hyperalgesia (OIH) is a very common consequence of pain management with opioids. Characteristics of OIH are worsening pain over time despite an increased dose of the opioid. It is often recognized neither by the physician nor the patient, and it results in increasing doses of opioid medications and continued unsatisfying pain levels experienced by the patient. The increased use of narcotics has a negative impact on patient outcome, as patients suffer from increased pain levels and often develop depression. Patients with OIH require frequent assessment for aberrant behaviors as an indicator of addictive use. Opioid-seeking behavior may complicate the clinical picture of failed opioid therapy. The treatment of OIH is to discontinue the opioid medication and to treat the patient's withdrawal symptoms, if necessary, in an inpatient setting with medical monitoring.

### **T31. PREVALENCE, COST OF CARE, AND TREATMENT PATTERNS FOR MAJOR DEPRESSIVE DISORDER RELATED HOSPITALIZATIONS**

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**Abstract:** Background: In addition to being a serious public health problem, major depressive disorder (MDD) is the most common primary diagnosis among psychiatric hospitalizations. These hospitalizations are a significant burden on healthcare systems, patients, and their families. However, there is limited information about the current duration and costs associated with MDD hospitalization and whether the presence of suicidal ideation or suicide attempt affects these measures.

Methods: An analysis of the Premier Perspective® Hospital Database was conducted using records of hospital admission for MDD on any date from January 1, 2014 to December 31, 2015. Hospitalizations had to have an admission diagnosis of single episode MDD (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis code 296.2 or 10th Revision [ICD-10-CM] code F32) or recurrent episode MDD (ICD-9-CM 296.3, ICD-10-CM F33). The presence of codes ICD-9-CM (V62.84) or ICD-10-CM (T14.91, X71.0XXA – X83.8XXS, Z91.5) defined suicidal ideation; codes ICD-9-CM (E950-E959) or ICD-10-CM (R45.851) defined suicide attempt. Length of hospital stay, cost of stay, intensive care unit (ICU) stay, attending physician specialty, and discharge status were analyzed.

Results: Of all hospital admissions during this period (N=12,608,691), 1.1% (N=136,704) were for MDD. Among MDD encounters, 53.7% had suicidal ideation (n=73,365) and 6.1% (n=8,374) had a suicide attempt. The percent of MDD stays requiring ICU bed days was 2.4% (no ideation/attempt, 1.6%; ideation, 2.7%; attempt, 4.6%). Nearly 90% of stays included dispensing of one or more major antidepressant therapies, with 63.6% of stays including a serotonin-norepinephrine reuptake inhibitor (SNRI), 58.5% a selective serotonin reuptake inhibitor (SSRI), and 44.1% an atypical antipsychotic (AAP). The mean length of hospital stay for all MDD encounters was 6.0 days (no ideation/attempt, 6.3 days; ideation, 5.9 days; attempt, 5.8 days); the mean cost per stay was \$6582 (no ideation/attempt, \$6863; ideation, \$6340; attempt, \$6861). In approximately 90% of MDD hospitalizations, regardless of suicide-

related status, the attending physician was a psychiatrist and the patient was discharged to home or self-care.

Conclusions: MDD-related hospitalizations are numerous and costly to healthcare systems. Medications that are currently used to treat MDD in the hospital setting (eg, SSRI, SNRI, AAP) take 4-6 weeks to reach maximum effect. In general, there is an unmet medical need for medications with a faster onset of action that may allow for shorter hospitalizations and lower costs. Such medications may be especially beneficial to patients with MDD who are hospitalized due to suicidal ideation or attempt.

### **T32. EX VIVO INFLAMMATORY RESPONSE PATTERNS AMONG NON-MEDICATED DEPRESSED PATIENTS**

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**Abstract:** Depression has been linked with numerous inflammatory medical conditions. Immune dysregulation is one pathway linking depression to negative health outcomes, with emerging evidence suggesting sex differences. Immune function can be quantified via stimulation of blood with a mitogen ex vivo, which indicates the capacity of immune cells to produce cytokines to immune challenge. Few studies have examined ex vivo inflammatory responses in depressed patients, and these studies have yielded mixed results. While some studies have shown increased proinflammatory cytokine release in depression, others have shown reduced production of proinflammatory cytokines, or no change. One reason for these inconsistencies might be that all studies had a single time-point of blood incubation. A broader pattern of inflammatory responses to immune challenge in depression over multiple time-points of blood incubation has never been examined.

Our goal in the present study was to examine basal inflammation and stimulated production of proinflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), anti-inflammatory cytokines (IL-4 and IL-10), and chemokines (IL-8 and MIP- $\alpha$ ) among non-medicated depressed patients compared to healthy controls over multiple time-points of blood stimulation (i.e., 2, 4, 8 and 24 hours).

This is an ongoing study. Subjects were recruited from central Pennsylvania (ages 18-25 years), assessed by a diagnostic psychiatric interview (Mini-International Neuropsychiatry Interview) and classified into healthy or depressed groups. Severity of depression was evaluated by a standard patient health questionnaire (PHQ-9). Healthy control subjects did not have a family history of major depression or major psychiatric illness. All depressed subjects were non-medicated. To determine stimulated cytokine levels, separate 1 ml aliquots of whole blood were incubated with 1  $\mu$ g/ml of bacterial lipopolysaccharide (LPS) for 2, 4, 8 or 24 hours. Basal and stimulated cytokines were quantified using multiplex bead arrays (Meso Diagnostics).

To date, 15 subjects (mean age=21, 60% women) have completed the study, providing limited data for analyses. We expect to have data available for at least 30 subjects by the time of the meeting. Preliminary analyses revealed a significant interaction of time x study group for LPS-stimulated IL-1 $\beta$  (F=4.96, p=0.04) and a marginally significant interaction for IL-10 (F=4.51, p=0.06), meaning that inflammatory responses to LPS differed between depressed subjects and non-depressed controls. Post hoc analyses revealed significant differences in stimulated levels of IL-1 $\beta$  and IL-10 at the 24-hr time-point; depressed subjects had lower stimulated levels of

IL-1 $\beta$  and higher stimulated levels of IL-10 compared to healthy subjects. These effects were observed more strongly in women than men. No other significant effects were observed. These highly preliminary findings support the notion that inflammatory responses to immunogenic challenge are altered in depressed subjects. Further, these findings suggest that inflammatory responses in depression vary by sex. How these results fit and add to the existing literature will be discussed.

### **T33. ADJUNCTIVE BREXPIPAZOLE EFFECTS ON WEIGHT ACCORDING TO ANTIDEPRESSANT TREATMENT (ADT) IN SHORT-TERM MAJOR DEPRESSIVE DISORDER STUDIES**

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**Abstract:** Background: Brexpiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and an antagonist at 5-HT<sub>2A</sub> and noradrenaline  $\alpha$ 1B/2C receptors, all at similar potencies. Brexpiprazole was approved in 2015 by the FDA for use as an adjunctive therapy to antidepressants (ADT) for the treatment of major depressive disorder (MDD) and for treatment of schizophrenia. Here, we evaluate the effect of adjunctive brexpiprazole on weight according to ADT in patients with MDD and inadequate response to ADT, based on three randomized, double-blind placebo controlled, short term trials (Pyxis, Polaris, Sirius [NCT02196506]).[1,2]

Methods: Included in this analysis are three 6-week, randomized, double-blind, placebo-controlled studies. Two studies assessed adjunctive brexpiprazole at fixed doses of 2 mg (Pyxis, Sirius) the third study assessed doses of 1 and 3 mg (Polaris). Patients were adults with MDD with an inadequate response to current ADT. Demographics and baseline clinical characteristics according to ADT were assessed. Incidence of patients with weight increase as a treatment emergent adverse event (TEAE), mean weight change, and clinically significant (>7%) weight changes, according to ADT were evaluated.

Results: A total of 1448 patients were included in the safety sample (adjunctive brexpiprazole 1-3 mg + ADT, n=835 and placebo + ADT, n=613). The majority (71%) of patients in the sample were female, mean age was 44.4 years old, and 85% were white. Clinical characteristics were similar among all treatment groups, with the exception of the brexpiprazole + escitalopram group in which the patients were, on average, in their current episode of MDD for longer compared with the total sample (18.4 vs 15.9 months) and the brexpiprazole + fluoxetine group in which patients were younger compared with the total sample (mean age: 41.9 vs 44.4 years old, respectively). The incidences of patients with weight increased as a TEAE were 4.4% (brexpiprazole + sertraline, n=114), 4.7% (brexpiprazole + escitalopram, n=170), 5.7% (brexpiprazole + fluoxetine, n=105), 6.5% (brexpiprazole + paroxetine CR, n=108), 6.8% (brexpiprazole + duloxetine, n=192), and 9.6% (brexpiprazole + venlafaxine XR, n=146). Least Square Mean change in weight from baseline to last visit was 1.3 kg (brexpiprazole + fluoxetine group), 1.3 kg (brexpiprazole + sertraline), 1.6 kg (brexpiprazole + escitalopram), 1.6 kg (brexpiprazole + duloxetine), 1.7 kg (brexpiprazole + venlafaxine XR), and 1.9 kg (brexpiprazole + paroxetine CR). Clinically significant weight increase in body weight from baseline to last visit was 0% (brexpiprazole + fluoxetine), 2.4% (brexpiprazole + escitalopram), 3.1% (brexpiprazole + duloxetine), 4.1% (brexpiprazole + venlafaxine XR),

4.4% (brexpiprazole + sertraline), and 4.6% (brexpiprazole + paroxetine CR). There were no marked changes in weight outcomes among individual doses of brexpiprazole.

Conclusion: In these short-term studies, adjunctive brexpiprazole was associated with a weight increase of 1.3 kg to 1.9 kg, depending on ADT. ADT selection appeared to have little impact on weight parameters in these studies.

#### **T34. LONG-TERM EFFICACY OF ADJUNCTIVE BREXPIPIRAZOLE IN MAJOR DEPRESSIVE DISORDER (MDD) – POOLED ANALYSIS OF TWO SHORT-TERM PLACEBO-CONTROLLED STUDIES AND OF AN OPEN-LABEL, LONG-TERM EXTENSION STUDY**

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**Abstract:** Background: Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and an antagonist at 5-HT<sub>2A</sub> and noradrenaline  $\alpha$ 1B/2C receptors, all at similar potency. Brexpiprazole is approved in the United States for the treatment of schizophrenia and for use as adjunctive treatment in MDD. Treatment guidelines emphasize that the ultimate goal of treatment in the acute phase of an MDD episode is to achieve sustained remission. Here, we describe the long-term efficacy of brexpiprazole used as adjunctive treatment in patients with MDD and inadequate response to antidepressant treatment (ADT) based on the data from two US pivotal studies and an open-label extension study.

Methods: In the two pivotal studies, patients with MDD and inadequate response to 1–3 ADTs were enrolled and received single-blind ADT for 8 weeks of prospective treatment. Patients with inadequate response during the entire prospective phase were randomized to ADT+brexpiprazole or ADT+placebo for 6 weeks. Both studies included fixed doses of brexpiprazole (2mg/day in the Pyxis study [1]; 1mg/day and 3mg/day in the Polaris study [2]). The open-label extension study was a flexible-dose (brexpiprazole 0.5–3 mg/day) study (Orion; NCT01360866) that enrolled patients who completed either of the two pivotal studies. The duration of the Orion study was originally designed to be 52 weeks, but was later amended to 26 weeks. As the two lead-in pivotal studies had a similar design, a post-hoc analysis was performed on the subgroup of patients who entered the open-label extension study. We evaluated the percentage of patients who achieved sustained remission, defined as a Clinical Global Impression – Severity (CGI-S) score  $\leq 2$  for at least 8 consecutive weeks. A Kaplan-Meier (KM) analysis was used to estimate the rate at which patients achieved sustained remission at Week 26 starting from the first dose of brexpiprazole.

Results: A total of 857 patients from Pyxis and Polaris entered the Orion study; of those, 522 patients had received adjunctive treatment with brexpiprazole in these lead-in studies. The KM estimate for the cumulative rate of sustained remission after 26 weeks of treatment with brexpiprazole was 32.4% (95% confidence interval: 28.2, 37.0).

Conclusion: The goal of treatment in MDD is to achieve sustained, long-term remission. Here, we show that after 6 months of adjunctive brexpiprazole treatment, 32.4% of patients achieved sustained remission, supporting the long-term efficacy of adjunctive brexpiprazole.

#### **T35. WHAT IS THE OVERLAP BETWEEN SUBJECTIVE AND OBJECTIVE COGNITIVE IMPAIRMENT IN MAJOR DEPRESSIVE DISORDER (MDD)?**

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**Abstract:** Cognitive impairments, such as memory deficits and executive impairment, have been commonly reported in major depressive disorder (MDD) and can be captured with either objective or subjective assessments. The advantage of assessing performance on standardized cognitive tests is that these are objective measures, relatively devoid of biases, but the norms for these measures are population-based and do not reflect premorbid performance levels. The advantage of using self-reported measures of perception of one's cognitive and executive function is that some of these measures, such as the cognitive and physical functioning questionnaire (CPFQ), capture the individual's perception of change from premorbid levels. However, the individual's affective and mood state may affect the perception of cognitive function. The aim of this post-hoc analysis of the CONNECT study was to assess the degree of overlap between subjective and objective cognitive impairment in a population of MDD patients, and to evaluate the associated clinical characteristics. As described in Mahableshwarkar et al. (Neuropsychopharmacology. 2015 Jul;40(8):2025-37), in the study called CONNECT, patients with MDD who subjectively reported cognitive dysfunction were randomly assigned to receive 8 weeks of double-blind treatment with flexible doses of vortioxetine (10 or 20 mg q.d.), placebo, or duloxetine 60 mg q.d., which was included as the active reference arm to ensure clinical assay sensitivity. At the end of the acute phase, a one-week, double-blind taper-down period was implemented following the acute treatment phase to address potential concerns regarding discontinuation symptoms with duloxetine treatment. The study was conducted between April 2012 and February 2014, enrolling a total of 602 patients. Efficacy was assessed using a battery of objective tests of cognitive function representing multiple domains: DSST performance (integrated cognitive functioning, including executive function, processing speed, attention, spatial perception, and visual scanning), Trail Making Test A (speed of processing), Trail Making Test B (executive functioning and speed of processing), Congruent and Incongruent Stroop Test (executive functioning selective attention, speed of processing), Groton Maze Learning Test (visual learning and memory), Detection Task (motor speed), Identification Task (attention), and One-Back Task (attention, working memory). The CPFQ was used for patient-reported assessments of cognitive function. All subjects underwent assessment of their depressive symptoms with the MADRS and Clinical Global Impressions. While 48% of the MDD patients met criteria for subjectively defined cognitive impairment, 64% of the MDD patients met our criteria for objectively defined cognitive impairment. Therefore, the proportion of patients defined as having impairment in cognition was somewhat similar regardless of the methodology. Overall, 80% of the MDD patients in this study reported either subjective or objective cognitive impairment. However, the proportion of patients meeting criteria for both subjectively and objectively defined cognitive impairment was only 31%. This post-hoc study shows that approximately 80% of MDD patients participating in an antidepressant trial reported either subjective or objective cognitive impairment.

**T36. METABOLIC AND CELLULAR DISTRESS GENE EXPRESSION PATTERNS ARE ASSOCIATED WITH TREATMENT RESISTANCE AND REVERSED BY DEEP BRAIN STIMULATION IN RODENT MODEL**

Kriti Gandhi\*, Sutor Shari, Mark Frye, Susannah Tye



**Abstract:** Treatment resistant depression is a major unmet need for which deep brain stimulation (DBS) is an emerging therapy. Physiologic mechanisms giving rise to antidepressant treatment resistance in depressive illness and the mechanisms underlying responses to DBS remain poorly understood. Using a genome-wide transcriptomics approach, we aimed to identify molecular pathways contributing to both antidepressant resistance and DBS efficacy in a preclinical model of antidepressant-resistance induced via chronic adrenocorticotrophic hormone (ACTH; 100µg; i.p.; 14 days). Animals were allocated to stress-naïve or forced swim test (FST) stress conditions and received either ACTH or saline (0.9%) control treatments. Additional groups received either imipramine or infralimbic (IL) DBS (n=7-8 per group). The infralimbic area was dissected and global gene expression profiles obtained for saline, ACTH and ACTH-DBS groups (Agilent). Gene set enrichment analysis (DAVID) was performed following Bonferroni correction and KEGG pathways were identified (Fisher exact score  $p < 0.05$ ). In antidepressant-resistant groups, significant increases in genes involved in metabolism and cellular survival were observed, and in antidepressant-resistant groups treated with DBS, increased expression of genes involved in cell proliferation, survival, inflammation and metabolism were seen. Cellular distress molecular patterns indicative of oxidative stress, hypoxia, endoplasmic reticulum stress, pro-inflammatory cytokines, nutrient deprivation and DNA damage were increased in the treatment-resistant group and attenuated by DBS ( $p < 0.05$ ). Thus, development of antidepressant resistance may relate to reduced cellular capacity adaptation to stress, and DBS may help to restore and overcome mechanisms contributing to cellular distress. This may help initiate longer-term neural adaptations that contribute to treatment efficacy in DBS therapeutics for depression and may be used to further optimize DBS mechanism(s) of action and identify novel specific therapeutic targets.

### **T37. ADJUNCTIVE BREXPIRAZOLE IN PATIENTS WITH MDD AND ANXIETY SYMPTOMS: RESULTS FROM POST-HOC ANALYSES OF THREE PLACEBO-CONTROLLED STUDIES**

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**Abstract:** Background: Symptoms of anxiety are prevalent in Major Depressive Disorder (MDD) and are associated with greater illness severity, suicidality, impaired functioning and poor response to antidepressant treatment (ADT). The presence of anxiety symptoms in MDD can be assessed using different definitions, e.g., anxious depression (score  $\geq 7$  on the HAM-D anxiety/somatization factor, as defined by the STAR\*D investigators [1]), or using the new DSM-5 specifier “anxious distress”. Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and an antagonist at 5-HT<sub>2A</sub> and noradrenaline  $\alpha$ 1B/2C receptors, all at similar potency. Brexpiprazole is approved in the United States for treatment of schizophrenia and for use as adjunctive treatment in MDD. The objective of the post-hoc analyses presented here was to assess the efficacy of adjunctive brexpiprazole when added to an ADT in patients with MDD and anxiety symptoms using two definitions: 1) Anxious distress; 2) Anxious depression.

Methods: Data from three randomized, double-blind, placebo-controlled studies with similar design were pooled for these analyses (Pyxis - NCT01360645; Polaris - NCT01360632; Sirius - NCT02196506). In the three studies, patients with MDD and an inadequate response to 1-3 ADTs were enrolled and received single-blind ADT for 8 weeks. Patients with inadequate

response throughout this prospective phase were randomized to ADT+brexpiprazole (2mg in Pyxis and Sirius; 1mg or 3 mg in Polaris) or ADT+placebo for 6 weeks. Proxies were used to categorize patients as having anxious distress if they had  $\geq 2$  of the following symptoms; tension (MADRS item 3 score  $\geq 3$ ), restlessness (IDS item 24 score  $\geq 2$ ), concentration (MADRS item 6 score  $\geq 3$ ), or apprehension (HAM-D item 10 score  $\geq 3$ ) at randomization [2]. Scores on the specific items of the HAM-D anxiety/somatization factor at randomization (baseline) were used to identify patients with anxious depression. The efficacy endpoint was the change in MADRS total score from baseline to Week 6. The analyses were conducted using a Mixed Model Repeated Measure (MMRM) approach with all brexpiprazole doses pooled.

Results: After 8 weeks of prospective ADT monotherapy, a total of 57.6% (n=797/1383) and 48.5% (n=671/1383) of the patients who were randomized met the criteria for having anxious distress or anxious depression, respectively. The mean MADRS total score was 29.0 and 29.1 for patients with anxious distress in the adjunctive brexpiprazole (n=462) and placebo (n=327) groups, respectively, and 28.9 (brexpiprazole; n=384) and 28.6 (placebo; n=282) for patients with anxious depression. Adjunctive brexpiprazole showed greater improvement than adjunctive placebo in the change from baseline to week 6 in the MADRS total score in patients with anxious distress (least square mean difference -2.38, p=0.0001), and in patients with anxious depression (-1.68, p=0.0116). Similar effects were observed in patients without anxious distress (-1.40, p=0.0226) or without anxious depression (-2.17, p=0.0002).

Conclusion: The present data suggest that adjunctive brexpiprazole may be efficacious in reducing depressive symptoms in patients with clinically relevant symptoms of anxiety.

### **T38. ACUTE KETAMINE ADMINISTRATION CORRECTS ABNORMAL INFLAMMATORY BONE MARKERS IN MAJOR DEPRESSIVE DISORDER**

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**Abstract:** Background: Patients with MDD have clinically relevant, significant decreases in bone mineral density and experience increased fracture rates RANKL is the principal osteoclastogenic factor, OPG is a decoy receptor for RANKL, and OPN plays a significant role in bone strength. We aimed to determine the OPG/RANKL ratio, predictive of bone growth, and OPN levels were different in patients and controls, and whether ketamine significantly influenced their levels.

Methods: Samples of 44 subjects with treatment-resistant major depressive disorder (n=28) or healthy control (HC) (n=16) were included in the study. Each study was a double-blind, randomized, placebo-controlled, cross-over trial assessing the antidepressant efficacy of acute ketamine infusion.

Results: Compared to controls, patients with MDD had significantly reduced OPG/RANKL ratio and decreased plasma OPN levels. Ketamine infusion restored the OPG/RANKL ratio and plasma OPN levels to normal at MDD subjects. Ketamine had no effects on either parameter in healthy controls.

Conclusions: Our study has several clinical implications. Decreases in the RANKL/OPG ratio could be an important factor in the osteoporosis of depression. The reduction of OPN in depressed subjects should be conducted in a larger group, especially postmenopausal women who frequently suffer bone fractures. The capacity of ketamine to restore the OPG/RANKL

ratio to normal as well as normalize the decreased OPN levels and decrease RANKL indicates that ketamine in addition to its potent mood effects, may also help ameliorate a serious medical complication of depressive illness.

**T39. A BREATHING-BASED MEDITATION INTERVENTION FOR PATIENTS WITH MAJOR DEPRESSIVE DISORDER FOLLOWING INADEQUATE RESPONSE TO ANTIDEPRESSANTS: A RANDOMIZED PILOT STUDY**

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**Abstract:** Objective: To evaluate feasibility, efficacy and tolerability of Sudarshan Kriya yoga (SKY) as an adjunctive intervention in patients with major depressive disorder (MDD) with inadequate response to antidepressant treatment.

Method: Patients with MDD (defined by DSM-IV-TR) depressed despite  $\geq 8$  weeks of antidepressant treatment were randomized to SKY or a waitlist control (delayed yoga) arm for 8 weeks. The primary efficacy end point was change in 17-item Hamilton Depression Rating Scale (HDRS-17) total score from baseline to 2 months. The key secondary efficacy end points were change in Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) total scores. Analyses of the intent-to-treat (ITT) and completer sample were performed. The study was conducted at the University of Pennsylvania between October 2014 and December 2015. Results: In the ITT sample (n=25), the SKY arm (n=13) showed a greater improvement in HDRS-17 total score compared to waitlist control (n=12) (-9.77 vs. 0.50,  $P = .0032$ ). SKY also showed greater reduction in BDI total score versus waitlist control (-17.23 vs. -1.75,  $P = .0101$ ). Mean changes in Beck Anxiety Inventory (BAI) total score from baseline were significantly greater for SKY than waitlist (ITT mean difference: -5.19; 95% CI -0.93 to -9.34;  $P = .0097$ ; completer mean difference: -6.23; 95% CI -1.39 to -11.07;  $P = .0005$ ). No adverse events were reported.

Conclusion: Results of this randomized, waitlist-controlled pilot study suggest the feasibility and promise of an adjunctive SKY-based intervention for patients with MDD who have not responded to antidepressants.

**T40. A NOVEL APPROACH TO RELAPSE PREVENTION STUDIES IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A PHASE 4 STUDY WITH VORTIOXETINE**

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**Abstract:** Major depressive disorder (MDD) is a chronic, episodic condition. Patients often require life-long treatment, first to achieve remission and then to prevent relapse. Here we compare the traditional relapse prevention study design with a recently employed study designed to evaluate vortioxetine for the prevention of relapse over a range of doses.

Vortioxetine is a multimodal antidepressant with activity at multiple serotonin receptors in addition to reuptake inhibition, resulting in the modulation of multiple neurotransmitters. The efficacy of vortioxetine for the prevention of relapse was initially demonstrated in a study that followed a traditional randomized withdrawal study design [1,2]. Patients with active

depression first received open-label flexible-dose treatment (5 or 10 mg/day) with vortioxetine, and those who achieved remission at both weeks 10 and 12 were randomized to double-blind placebo or vortioxetine, continuing on the same 5- or 10-mg dose with which they achieved remission. Patients were then observed for a predetermined time (24-64 weeks) or until they relapsed. In the primary analysis of time to relapse, vortioxetine was significantly favored over placebo, with those treated with placebo twice as likely to relapse during the double-blind treatment period [1]. However, while higher doses of vortioxetine have exhibited better acute treatment effects, whether there is a dose-dependent effect with regard to relapses was not addressed.

In a new relapse prevention study (ClinicalTrials.gov ID: NCT02371980), approximately 1100 patients will receive a fixed dose of vortioxetine at 10 mg/day in a longer open-label period of 16 weeks. Approximately 600 patients who respond and are in remission after acute treatment at 10 mg/day will be randomized to 1 of any 4 treatment arms (5, 10, 20 mg vortioxetine or placebo). In contrast to previously conducted prevention studies, the current study design provides the opportunity to explore any dose-dependent effect in the prevention of relapse rates.

The design of this study however presents some challenges. After the fixed-dose phase in which a patient is stabilized, the randomization to a different active dose may lead to reduced efficacy or increased side effects if the dose is lower or higher, respectively. To address this point, in the present study, a fixed dose of 10 mg during the open-label period will help mitigate tolerability and/or efficacy issues associated with these large dose adjustments. However, the risks associated with changing doses still remain.

The findings from this new study design may have implications for regulators, prescribers, and patients alike, as well as developers of new drugs for chronic conditions. For example, if lower doses (5 or 10 mg) of vortioxetine are found to be equally efficacious as the 20-mg dose in the prevention of relapse, prescribers may be able to reduce the patients' treatment dose after remission and patients may experience fewer tolerability issues while maintaining remission, resulting in improved adherence to treatment and overall quality of life.

#### **T41. RELATIONSHIP BETWEEN SEXUAL ABUSE AND SUICIDALITY: WHAT IS THE EVIDENCE?**

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**Abstract:** Suicidal thoughts and/or behaviors represent psychological consequences for some victims of sexual abuse or assault. Methodological limitations for collecting sexual abuse history as well as assessing suicidal risk have been noted in the research literature. A secondary analysis was conducted to describe the prevalence of sexual abuse among a sample of adult, psychiatric inpatients and determine whether sexual abuse history, for men and/or women, served as a significant predictor to suicidal behavior. Nearly half of the sample reported lifetime sexual abuse, which was found to be a significant risk factor for suicidal behavior in the clinical sample. Systematic inquiry is needed when collecting patient histories regarding sexual abuse with awareness to any possible gender bias.

**Introduction:** Sexual abuse is a traumatic experience with possible consequences including suicidal thoughts and/or behaviors (e.g., 1, 2, 3). Current literature examines characteristics and correlates with age, gender, sexuality, psychiatric or community samples, and type of abuse. A greater proportion of women report having a history of sexual abuse than men. Gender biases, biased item language, lack of systematic inquiry, and perceived discrimination may contribute to lower prevalence among men due to under-reporting. Clinical researchers have raised awareness of the methodological limitations of suicide assessment procedures (4).

**Methods:** N = 199 adult psychiatric inpatients from original psychometric evaluation study. Innovative secondary analysis due to research methodology: (a) in-person semi-structured, systematic suicide assessments and (b) general non-biased item on lifetime sexual abuse.

**Measures:** Self-report demographic questionnaire (gender); Columbia-Suicide Severity Rating Scale (5) (lifetime suicidal ideation, attempts); risk assessment interview (sexual abuse history: "Have you ever had any unwanted sexual experiences?").

**Results:** 45% (n = 90) of the clinical sample reported lifetime history of sexual abuse. No significant difference between genders on total lifetime attempts (p = .402). Logistic regression analysis revealed history of sexual abuse significantly predicted history of suicide attempt,  $b = .87 (\pm .34)$ , Wald = 6.77, p = .009. After controlling for sexual abuse, there was no significant gender effect or interaction between gender and sexual abuse predicting lifetime suicide attempt (both p > .380).

**Discussion:** Sexual abuse is significant risk factor for suicidality for an adult psychiatric inpatient sample. Evidence for this risk factor predominately limited to women, community samples (e.g., college students). While gender differences remained consistent with existing literature, high prevalence of men reporting sexual abuse warrants further investigation. Clinicians should sensibly and systematically inquire about previous sexual abuse in psychiatric patients when assessing for suicidal risk behaviors because in this sample of psychiatric inpatient adults, 95% of patients reported lifetime suicidal ideation. Clinicians should self-evaluate preconceived notions about sexual abuse victims and ask open-ended gender-neutral questions to avoid bias.

#### **T42. NEUROCHEMICAL ALTERATIONS FOLLOWING SUPPLEMENTATION WITH A PUTATIVE CALORIC RESTRICTION MIMETIC BLEND OF NUTRIENTS AND PHYTOCHEMICALS**

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**Abstract:** Background: Caloric restriction (CR) without malnutrition has been consistently shown to increase longevity and lifespan in a broad range of species. Recent studies in a long-living rodent model suggest that CR can preserve brain mitochondrial function by altering neuroenergetics. These findings are translationally relevant since CR has been associated with improvements in working memory, executive function and cognitive function in elderly humans [1]. However, the neurochemical effects of CR are unknown. Most of the studies reporting beneficial effects of CR in animal models have employed 30% reduction in calories over a period of at least 3 months, which may be too stringent for humans to adhere to. Thus,

there is an unmet need for nutritional supplements, which can mimic the biological effects of CR, without the need for calorie or energy limitations. In an effort to meet this need, a formula consisting of ingredients selected on the basis of producing gene expression changes in mouse tissue that were similar to those seen with CR was designed. The ingredients of the supplement are: concentrated fish oil (Eicosapentaenoic acid & Docosahexaenoic acid), citrus bioflavonoids (naringin & hesperidin), purple corn extract including anthocyanins, alpha-lipoic acid, quercetin, d-limonene, rosemary extract (carnosic acid), resveratrol, coenzyme Q10, vitamin D3, vitamin K2 (menaquinone-7), lycopene, lutein and astaxanthin.

**Goal and Hypothesis:** The goal of the study was to investigate the effects of the blend of nutrients and phytochemicals, a putative CR mimetic, on neurochemistry. We hypothesized that supplementation will result in alterations in levels of (a) N-Acetylaspartate (NAA- a marker of neuronal integrity) (b) glutathione (GSH-a marker of antioxidant status).

**Methods:** The current study used a double blind, placebo-controlled design to investigate the effectiveness of a nutritional supplement, which mimics CR, on neurochemistry after 6 weeks of supplementation. Healthy middle-aged adults (N=61, age: 40-60 years) underwent proton magnetic resonance spectroscopy (1H MRS) at 3T at the beginning and end of the study period to investigate changes in brain chemistry.

**Results:** We observed an increase in N-acetylaspartate (NAA) in females as well as an increase in Glutathione (GSH)/Creatine (Cre) for males and females in the supplement group. Further, the supplement group also showed an increase in Glutamate (Glu)/Glutamine (Gln) ratio, which may suggest an increase in energy turnover [2].

**Conclusion:** The present study reveals that 6-weeks of daily supplementation of a blend of nutrients and phytochemicals, elicited changes in brain neurochemistry, increased NAA/H<sub>2</sub>O, GSH/Cre and Glu/Gln ratios in healthy middle-aged adults, in a manner which would be predicted with CR. To the best of our knowledge, this is the first study, which has identified neurochemical effects of a putative CR mimetic in healthy middle-aged humans. This study may be one of the first steps in establishing benefits of CR mimetics, thus underscoring the importance of development of such compounds.

#### **T43. A MULTICENTER, 8-WEEK, OPEN-LABEL STUDY TO ASSESS USABILITY OF A DIGITAL MEDICINE SYSTEM IN ADULT PATIENTS WITH SCHIZOPHRENIA TREATED WITH ORAL ARIPIPRAZOLE**

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**Abstract:** Background: A Digital Medicine System (DMS) has been developed to objectively measure and report a patient's medication ingestion. The DMS consists of a medication-embedded ingestible sensor, wearable sensor (adhesive patch), and mobile- and cloud-based software applications that enable the secure collection and sharing of objective medication adherence information with healthcare professionals (HCP).

**Objective:** To test the functionality of an integrated call center for the DMS in adult subjects with schizophrenia (SCH), bipolar 1 disorder (BP1) or major depressive disorder (MDD) who are treated with oral aripiprazole. The integrated call center operationalizes coordinated

feedback to the subject and investigative site to optimize the use of the DMS as measured by inbound calls (patient to call center) and outbound calls (call center to patient) by help type.

**Methods:** The study consisted of four US sites that enrolled patients with SCH, BP1, or MDD stabilized on oral aripiprazole. The study comprised 3 phases: up to 1-week screening phase, a 2-week prospective phase in which subjects who demonstrated  $\geq 50\%$  patch wear during week 2 (last 7 days before visit) continued to a 6-week observational phase with site visits at week 4 and 8. The primary outcome was the establishment of a functional and operational integrated call center with coordinated feedback to the subject and investigative site to optimize the use of the DMS as measured by inbound and outbound calls by help type. We measured the proportion of time during the trial period when the subject wears their patch, and an ingestion adherence defined as the total number of ingested events registered on the digital health server divided by the number of treatment days in the trial with good patch coverage. NCT02722967

**Results:** 51 patients were screened and 49 enrolled; 38/49 (77.6%) completed the study. The most common reason for discontinuation, per study design, was noncompliance with patch wear 4/49 (8.2%) at Week 2. No differences in completion rates were observed among patients with SCH 11/15 (73.3%), BP117/22 (77.3%) or MDD 10/12 (83.3%). The most common inbound calls were for technical questions with 37.5% (51/136) related to the pill status icon on the software application. The majority (55.3%, 142/257) of outbound calls were related to issues with the patch. Mean patch wear was 78% and mean ingestion adherence was 89% (in the days with good patch coverage) for all patients over the course of the 8-week study; no differences were observed among patients with SCH, BP1, or MDD

**Conclusions:** The results build on the utility of a DMS to objectively measure adherence in clinical practice suggesting that proactive calls to patients who do not have pill ingestion registered may be helpful in remediating issues with use of the patch.

**Disclosure:** Supported by Otsuka Pharmaceutical Development & Commercialization, Inc.

#### **T44. A CLASSIFICATION OF SUICIDALITY DISORDER PHENOTYPES**

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**Abstract:** Objective: To provide a classification of suicidality disorder phenotypes. The view that suicidality is trans-nosological and that all forms of suicide are the same, is not consistent with response to pharmacological treatment evidence. For example, antidepressants make suicidality better in some patients, worse in others, and are no better than placebo for a third group. This suggests that there may be more than one type of suicidality.

**Design:** We used a phenomenological approach by observing in detail and directly communicating with subjects over time about their suicidality.

**Results:** We developed diagnostic criteria and a related structured diagnostic interview for 12 distinct suicidality disorder phenotypes. 1) Impulse Attack Suicidality Disorders, 2) Homicidal Suicidality Disorders, 3) Psychotic Suicidality Disorders, 4) Obsessive Compulsive Suicidality Disorders, 5) PTSD Suicidality Disorders, 6) Eating Disorder / Malabsorption Suicidality Disorders, 7) Substance Induced Suicidality Disorders, 8) Medical Illness / Neurological Condition Induced Suicidality Disorders, 9) Anxiety Disorder Induced Suicidality Disorders, 10) Mood Disorder Induced Suicidality Disorders, 11) Life Event Induced Suicidality Disorders, and 12) Suicidality Disorders, Not Elsewhere Classified. Among these phenotypes,

the description of Impulse Attack Suicidality Disorder is new. This disorder is associated with unexpected, unprovoked, unpredictable attacks of an urgent need to kill oneself.

Conclusion: We offer 12 suicidality disorder phenotypes. Because these phenotypes may have a different response to treatment, each phenotype should be investigated separately when investigating anti-suicidality treatments and when investigating the relationship between genetic and other biomarkers in suicidality.

#### **T45. MEDICATION NON-ADHERENCE IN OLDER PATIENTS PRESCRIBED ANTIPSYCHOTIC MEDICATIONS**

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*Ingenuity Health*

**Abstract:** Introduction: Maintenance of antipsychotic drugs (APDs) is critical in the management of patients with serious mental illness in preventing relapse. Although older patients have better adherence rates compared to younger patients, lack of adherence remains a concern. The objective of the study is to assess factors associated with potential non-adherence of prescribed antipsychotic medications in older patients.

Materials and Methods: From 2013 to 2016, 2113 urine samples were obtained from patients, aged  $\geq 65$ , who were prescribed APDs. Samples were classified as APD positive (a positive LC/MS/MS result for APD parent and/or metabolite) or APD negative (negative LC/MS/MS). Samples were also classified as positive or negative for: non-prescribed opiates, synthetic opioids or benzodiazepines, cocaine and THC. Logistic regression analyses were used to calculate odds ratios and 95% CIs. Because data were obtained from a de-identified database, this study was not submitted for IRB review.

Results: The study population was 35.7% male with a mean age of  $69.1 \pm 4.4$  years. Prescribed single APD therapy included quetiapine (27.8%), aripiprazole (20.6%), risperidone (17.3%), olanzapine (13.7%), paliperidone (2.8%), ziprasidone (3.6%), haloperidol (3.4%), and clozapine (1.7%); with 9.3% prescribed multiple APDs. Urine testing was positive for APD in 82.9% of samples and negative in 17.1%, and varied widely by prescribed drug. Patients prescribed ziprasidone, or multiple APDs had the highest rate of negative samples (27.6% and 27.0% respectively); with those on quetiapine aripiprazole, haloperidol and risperidone being in the mid-range (21.2%, 18.6% 16.9% and 11.5%, respectively), whereas samples from those on paliperidone, olanzapine and clozapine were least commonly negative (8.6%, 7.9% and 2.9%, respectively). APD negative individuals were more likely than APD positive to have a non-prescribed opiate/synthetic opioid found (21.9% vs. 11.3%; OR, 2.2; 95% CI, 1.6-3.0) as well as a non-prescribed benzodiazepine (9.8% vs. 6.0%; OR, 1.7; 95% CI, 1.1-2.6). A non-prescribed APD was found in 4.8% of samples, with paliperidone being the most commonly detected (2.1%). THC or cocaine was found in 3.9% and 1.2% of samples, respectively.

Conclusions: These data suggest that urine drug monitoring in older patients who are prescribed APDs can be of value in both monitoring adherence to APD therapy, and in identifying the use of inappropriate prescription and non-prescription substances. The data also suggest that non-adherence to prescribed APD therapy is associated with use of non-prescribed opioids and benzodiazepines.



## **T46. NIMH IRP TRANSLATIONAL NEUROPSYCHOPHARMACOLOGY INITIATIVE**

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*NIMH/NIH*

**Abstract:** Background: The need for novel therapies for central nervous system (CNS) disorders with improved efficacy, safety, and tolerability is unquestionably high, as it is widely recognized that, despite currently recognized treatments, CNS disorders are major contributors to the global burden of illness and incur high economic costs. Unfortunately, over the past two decades, CNS drug discovery has been, with a few exceptions, relatively unsuccessful in delivering new chemical entities especially for the treatment of psychiatric disorders. The National Institute of Mental Health (NIMH) has become increasingly aware of the reduced investment by pharmaceutical companies in the development of therapeutics for treating psychiatric disorders despite the unmet medical need. In response to the reduced efforts in the pharmaceutical industry towards psychiatric drug discovery the NIMH Intramural Research Program (IRP) is proposing to re-invigorate psychiatric drug discovery by facilitating and de-risking the discovery and development of novel treatments. Support for the discovery and development of new treatments for psychiatric disorders including target validation, biomarker development, IND enabling studies, and Phase I safety / tolerability and Phase II proof of concept studies are all in scope for this important NIMH IRP initiative.

Methods: After completing a confidentiality agreement, interested parties including academic groups, small and large pharma or biotech may apply by submitting a proposal including detailed information on: the psychiatric indication, therapeutic rationale, target engagement, current stage of development, a development plan, project milestones, intellectual property and patent landscape, future objectives and anticipated outcomes. In addition, a compound 'report card' with details on the chemical properties of the compound of interest is completed and submitted with each proposal.

Results: To steer this initiative the NIMH IRP has established the NIMH Translational Neuropsychopharmacology Task Force (TNTF). The TNTF is comprised of a panel of neuroscience drug discovery/development experts from the pharmaceutical industry and the NIH who prioritize, critically review, and recommend new proposals for support to the NIMH IRP Leadership. Supported proposals will either be sourced by NIMH IRP Principle Investigators and Staff or the desired work may be supported by outsourcing under the direction of the IRP. The NIMH IRP has experience in the clinical testing of novel therapies for the treatment of psychiatric diseases including generalized anxiety disorder (GAD), treatment resistant depression (TRD), bipolar disorder (BPD), perimenopausal depression (PMD). In addition, the NIMH IRP has extensive CNS imaging capabilities including PET and fMRI that are readily integrated into clinical studies to answer questions regarding target engagement or better understand disease pathology.

Discussion: The NIMH is committed to engaging with the scientific community and reinvigorating the development of new therapies for the treatment of psychiatric disorders. The current reduction in psychiatric drug discovery and development in the pharmaceutical industry provides an opportunity for the NIMH IRP to contribute in an important way to de-risking novel therapeutics and engage industry in an effort to get more effective treatments to patients.

## **T47. RATIONALE FOR THE CLINICAL DEVELOPMENT OF ITI-214, A PDE1 INHIBITOR**

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**Abstract:** Background: Enzymes of the PDE1 family are calcium/calmodulin activated cAMP/cGMP hydrolases. Active in stimulated or pathological conditions when intra-cellular calcium levels rise, these enzymes exert little influence on basal cellular cyclic nucleotide levels. Consequently, PDE1 inhibitors function to restore normal signaling for both CNS and non-CNS disorders in pathological states, particularly in those states accompanied by high intracellular calcium levels. PDE1 inhibitors have minimal influence in nonpathological states. Intra-Cellular Therapies has developed a portfolio of PDE1 inhibitors, of which ITI-214 is the most advanced and has completed 4 Phase 1 clinical studies. The mechanism of action of ITI-214 and its activity in animal models suggest therapeutic potential for a variety of CNS and non-CNS diseases.

Methods: ITI-214 has been tested in panels of PDEs, GPCRs, and key enzymes. ITI-214 has been tested in a rodent model of novel object recognition to evaluate cognitive effects. ITI-214 was evaluated behaviorally in the step-down latency test of catalepsy in mice. Anti-parkinsonian effects in mice treated unilaterally with 6-hydroxydopamine (6-OHDA) were evaluated using the cylinder test to assess contralateral limb use in the presence and absence of dopamine replacement. Wakefulness and locomotor activity in mice was measured with telemetry.

Results: With 1000-fold selectivity for PDE1 compared with the next nearest PDE family enzyme, ITI-214 has no significant off-target effects when screened against a panel of 70 key receptors & enzymes. ITI-214 has shown activity in rodent models of motor and non-motor symptoms in Parkinson's disease. ITI-214 was able to reverse haloperidol-induced catalepsy; unlike inhibitors of PDE4 and PDE10 (eg. rolipram and papaverine), ITI-214 did not exacerbate catalepsy induced by dopamine antagonism. ITI-214 was also able to reverse reserpine-induced catalepsy. In mice lesioned unilaterally with 6-OHDA, ITI-214 treatment restored contralateral limb use. In this latter model ITI-214 potentiated subthreshold doses of L-DOPA, suggesting that it could be used clinically to reduce the L-DOPA dose. In lesioned mice receiving chronic L-DOPA, PDE1 inhibitors reduced established dyskinesia. Active versus non-motor deficits of Parkinson's disease, ITI-214 was able to improve memory in the novel object recognition model of memory performance. Analogues of ITI-214 have shown dose dependent increases in wakefulness without effects on general locomotion. Finally, ITI-214 has shown anti-inflammatory effects in a number of animal models.

ITI-214 has been tested in 4 Phase 1 clinical trials. This program included a single rising dose study in normal healthy volunteers, a multiple dose study in which ITI-214 was administered daily over 14 days to healthy volunteers and patients with stable schizophrenia, a study (conducted in Japan) in which ITI-007 was administered for 7 days at multiple rising oral doses, and a bioequivalence study. In all 4 Phase 1 studies, ITI-214 demonstrated a favorable safety profile and was generally well tolerated in both healthy volunteers and patients with schizophrenia. Pharmacokinetic evaluation indicated once-a-day dosing. Analysis of cerebrospinal fluid concentration in the multiple dose study indicated measurable drug concentration demonstrating ITI-214 crosses the blood brain barrier.

Discussion: ITI-214 represents a novel approach for the treatment of CNS and non-CNS disorders with potential utility in a number of indications including Parkinson's disease (motor

and non-motor aspects), cognitive enhancement in schizophrenia, Parkinson's and Alzheimer's disease, ADHD and neuroinflammatory disease.

#### **T48. PERSONAL EXPERIENCES WITH THE DIGITAL MEDICINE SYSTEM – A CASE SERIES**

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**Abstract:** Introduction: The medical community widely recognizes that non-adherence to prescribed antipsychotic medication in those with serious mental illness (SMI) is associated with suboptimal outcomes, increased morbidity in an already vulnerable population and increased cost to society. The novel Digital Medicine System (DMS) holds the promise of addressing the fundamental adherence problem by objectively measuring medication ingestion, while taking into account the limitations and special needs of those with SMI. The DMS consists of an ingestible sensor-embedded medication, a wearable sensor (adhesive patch), and mobile and cloud-based software applications that enable the secure collection and sharing of reliable medication adherence information with healthcare professionals (HCP).

Objectives: Obtain feedback of the subjective experiences and the reflections of two study participants with SMI, as well as that of the investigator, after having used the DMS to complement objective study data.

Methods: A selection of subjects' accounts of their experiences were obtained from clinical investigators, who described the patients' subjective experiences using the DMS, including specific challenges they faced and how those challenges were overcome. The accounts were drawn from investigators participating in 2 clinical studies around the usability of the DMS (NCT02219009, NCT02722967). Representative cases of a patient with schizophrenia and another with bipolar disorder were among those chosen to illustrate their experiences.

Findings: Subject S (patient with schizophrenia) initially struggled to become familiar with the system, but he became proficient within a few weeks despite having no prior experience with a smartphone. He had good adherence to study medication (aripiprazole), and his previous residual symptoms of schizophrenia (that included auditory hallucinations and paranoia) achieved resolution. He became more focused on his health and engaged in behaviors that likely supported better control of another chronic medical condition. He expressed having a personal sense of accomplishment, and an appreciation for how he was able to work with his health providers while using the DMS.

Subject B (patient with bipolar disorder) had no difficulties learning to use the DMS, though he expressed wanting changes to the patch size and expansion of features such as medication tracking and healthy activity reminders. His adherence with taking medication improved, which was attributed in part to the use of reminders and the benefits of establishing a routine. He also reported that he was better able to remember to pick his younger children up from school and to exercise daily. The experiences of additional participants will be elucidated in the poster.

Conclusions: Participants and investigators reported that the participants experienced overall minimal difficulty in learning to use the DMS, which they were able to overcome. They had

significant improvement in adherence to taking antipsychotic medication. In addition, it was reported that the DMS helped facilitate participants' efforts to engage in healthy behaviors. The studies were funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

#### **T49. SUBGROUP ANALYSES OF BASELINE CHARACTERISTICS AND TREATMENT RESPONSE TO LISDEXAMFETAMINE VS PLACEBO IN ADULTS WITH BINGE EATING DISORDER**

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**Abstract:** Introduction: Binge eating disorder (BED) is newly recognized so its characterization is important. Examining baseline characteristics and treatment responses of subgroups of individuals with BED will advance insight into the disorder.

Objective: To examine baseline characteristics and treatment responses to lisdexamfetamine (LDX) in adults with moderate to severe BED based on age and gender from 2 identically designed phase 3, double-blind trials of LDX.

Methods: Adults (18–55 years) with moderate to severe BED ( $\geq 3$  binge eating [BE] days/week and Clinical Global Impression–Severity scores  $\geq 4$ ) were eligible. Participants were randomized 1:1 to 12 weeks of dose-optimized LDX (50 or 70 mg/d) or placebo (PBO). For these post hoc analyses, data from the safety analysis sets and full analysis sets (FAS) were pooled across studies and examined descriptively by age ( $<40$  vs  $\geq 40$  years old) and gender (male vs female).

Results: The pooled safety analysis set and FAS, respectively, included 398 and 386 participants  $<40$  years old, 347 and 338 participants  $\geq 40$  years old, 105 and 97 men, and 640 and 627 women. Most participants in the pooled safety analysis set were white (range: 64.3%–77.5% across groups) and had a body mass index  $\geq 30$  kg/m<sup>2</sup> (range: 63.0%–75.5% across groups). In the FAS, the mean  $\pm$  SD number of BE days/week ( $<40$  years: PBO=4.57 $\pm$ 1.178, LDX=4.61 $\pm$ 1.232;  $\geq 40$  years: PBO=4.85 $\pm$ 1.449, LDX=4.86 $\pm$ 1.309; men: PBO=4.57 $\pm$ 1.457, LDX=4.68 $\pm$ 1.403; women: PBO=4.73 $\pm$ 1.299, LDX=4.73 $\pm$ 1.254) and Yale-Brown Obsessive Compulsive Scale modified for Binge Eating (Y-BOCS-BE) total scores ( $<40$  years: PBO=21.63 $\pm$ 4.616, LDX=21.51 $\pm$ 4.357;  $\geq 40$  years: PBO=21.40 $\pm$ 4.973, LDX=21.41 $\pm$ 5.033; men: PBO=20.42 $\pm$ 5.346, LDX=20.72 $\pm$ 4.422; women: PBO=21.70 $\pm$ 4.674, LDX=21.57 $\pm$ 4.702) were comparable across ages and genders at baseline. The least squares mean (95% CI) treatment difference (LDX–PBO) for the change from baseline in BE days/week at week 11–12 ( $<40$  years: –1.50 [–1.84, –1.17];  $\geq 40$  years: –1.50 [–1.90, –1.10]; men: –1.29 [–2.04, –0.53]; women: –1.55 [–1.83, –1.28]) and Y-BOCS-BE total score at week 12 ( $<40$  years: –7.92 [–9.37, –6.48];  $\geq 40$  years: –7.40 [–9.06, –5.73]; men: –5.95 [–8.95, –2.96]; women: –8.00 [–9.17, –6.83]) numerically favored LDX in all subgroups in the FAS. Higher percentages of participants were categorized as improved on the Clinical Global Impressions–Improvement (CGI-I) scale (scores of 1 [very much improved] or 2 [much improved]) at week 12/early termination with LDX compared with PBO across all subgroups ( $<40$  years: 85.4% vs 42.5%;  $\geq 40$  years: 82.4% vs 48.0%; men: 83.0% vs 50.0%; women: 84.2% vs 44.3%).

Conclusions: Across age and gender, participants exhibited comparable numbers of BE days/week and Y-BOCS-BE total scores at baseline. In addition, dose-optimized LDX

produced numerically greater reductions in BE days/week and Y-BOCS-BE total scores and improvement on the CGI-I than did PBO in each subgroup.

**T50. GLUCOSE METABOLISM AND BRAIN BIOENERGETICS MEASURED BY 31P MAGNETIC RESONANCE SPECTROSCOPY IN UNAFFECTED SIBLINGS OF PATIENTS WITH PSYCHOTIC DISORDERS**

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**Abstract:** Background: Increasing evidence suggests abnormal markers of energy metabolism both in brain and periphery in psychotic disorders. The present study examined peripheral glucose metabolism and aspects of brain bioenergetics and redox state in unaffected siblings of patients with first episode psychosis, compared to patients and healthy individuals.

Methods: 22 unaffected siblings, 18 first episode psychosis patients and 19 healthy controls were evaluated using an oral glucose tolerance test, with hemoglobin A1c measurement. Insulin sensitivity was estimated using the oral minimal model method. Lipid, leptin and inflammatory marker levels were also measured. Brain 31P magnetic resonance spectroscopy (31P-MRS) was performed in the frontal lobe on a 4T MR scanner, using a custom-designed dual-tuned surface coil. Brain parenchymal pH and measures of oxidative state (ratio of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and its reduced form (NADH)) were estimated from 31P-MRS. NAD<sup>+</sup> and NADH levels were determined using a 31P-MRS fitting algorithm. Results: Insulin sensitivity significantly differed among groups (patients < siblings < controls), with differences between patients and controls, and siblings and controls. There were no significant associations between insulin sensitivity and NAD<sup>+</sup>/NADH in patients, siblings or controls. Correlation coefficients between hemoglobin A1c and NAD<sup>+</sup>/NADH were significant in patients and controls, and approached, but did not attain statistical significance in siblings.

Conclusion: Patients and unaffected, untreated, siblings showed decreased insulin sensitivity compared to controls, suggesting abnormal glucose metabolism or a primary insulin signaling pathway abnormality related to risk and expression of psychosis. Furthermore, findings also suggest dynamic relationships between peripheral glucose metabolism and a specific redox state marker among unaffected siblings, patients and controls. Future treatment approaches to modulate brain bioenergetics, while improving glucose metabolism, may offer the possibility of improving brain function and body-wide bioenergetic abnormalities in psychotic disorders.

**T51. ANTI-TOXOPLASMA GONDII IGM IS POSITIVELY CORRELATED WITH SCORES ON THE NIH TOOLBOX FLANKER INHIBITORY CONTROL AND ATTENTION TEST IN PATIENTS WITH SCHIZOPHRENIA**

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**Abstract:** Introduction: Schizophrenia is associated with impaired cognitive function, which in turn is linked to deficits in functional outcomes including independent living. *Toxoplasma gondii* (*T. gondii*), a widespread neurotropic parasite, has been previously associated with schizophrenia. Findings from previous studies suggest that *T. gondii* impairs cognitive function but some studies have found no association between *T. gondii* and cognition while one study reported improved cognition after exposure to *T. gondii*. The aim of this study is to evaluate the association between *T. gondii* serointensity and cognition (specifically attention and inhibitory control) in a sample of patients with schizophrenia.

Methods: 106 patients with schizophrenia (mean age 33 (SD 12.3), 30 female and 76 male, 55 African-American, 33 Caucasian, 18 Hispanic or Asian) diagnosed with the Mini International Neuropsychiatric Interview version 5, were recruited. Anti-*T. gondii* IgG and IgM antibodies were measured in all the patients. Attention and inhibitory control were assessed utilizing the NIH Toolbox Flanker Inhibitory Control and Attention Test (FL). Pearson's correlation was used to evaluate the association between anti-*T. gondii* serointensity (IgG and IgM) and FL.

Results: Anti-*T. gondii* IgM serointensity (but not IgG) correlated with FL scores ( $r = 0.28$ ,  $p = 0.008$ ). Sex was found to be an effect modifier of the association (i.e. there was an interaction between anti-*T. gondii* IgM serointensity and sex [ $F = 6.52$ ,  $p = 0.002$ ]) such that the correlation was strong in male patients ( $r = 0.49$ ,  $p < 0.001$ ) but not significant in female patients ( $r = 0.08$ ,  $p = 0.709$ ).

Conclusions: The results are at odds with expected findings in line with tenets of parasitology that infection would lead to poor cognition and suggest that in male patients with schizophrenia, anti-*T. gondii* IgM serointensity is associated with improved attention and inhibitory control. These findings could be possibly explained by increase in dopamine upregulation associated with *T. gondii* infection via secretion of tyrosine hydroxylase in catecholaminergic neurons. Longitudinal studies are required to further evaluate the association between *T. gondii* serointensity and cognition by gender and race in patients diagnosed with schizophrenia.

## **T52. AUDIO VS. AUDIO-VIDEO RECORDING AS A QUALITY MEASURE IN SCHIZOPHRENIA CLINICAL TRIALS**

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**Abstract:** Introduction: As a quality assurance measure clinician administered interviews of efficacy measures are often recorded at the site for external independent review of interview quality and adherence to rating scale instructions. Audio reviews are sometimes preferred over audio +video because they are less intrusive and facilitate subject privacy. However, scales such as the Positive and Negative Syndrome Scale (PANSS) include numerous items that involve visual elements (eg, blunted affect, poor rapport, excitement) that cannot be thoroughly evaluated by audio recording. Due to the limitations of audio recording we hypothesized that inter-rater reliability between site raters and external reviewers of recorded interviews would be higher with audio + video than with audio alone.

Method: Data collected from 6 large clinical trials utilizing either audio+video review or audio only review were analyzed in the current post-hoc analysis. We have calculated the kappa values for each pair of site rater-independent rater ratings using the method developed to assess reliability when multiple raters assess a single case (Cicchetti et al. 2009). We have compared the mean kappa values for each of the PANSS items for which we had scores from both groups using two-group mean comparison t-test. As this is an exploratory analysis we did not apply a correction for multiple comparisons.

Results: 2849 interviews had scores from both, the site rater and the independent rater, 427 with audio review only and 2422 with audio+video. The overall kappa per rating pair was 0.72 in the audio+video group and 0.64 in the audio group only, the difference being statistically significant ( $p < 0.0001$ ). Out the 25 individual PANSS items where both audio+video or audio only review was available, 18 items had kappa values significantly higher in the audio+video group. The remaining items had their kappa values comparable between the groups.

Discussion: Agreement between site raters and independent reviewers was statistically significantly higher with audio+video than with audio alone. Audio recording of interviews for quality assurance purposes provides a relatively non-intrusive, privacy friendly means of evaluating interview quality and adherence to rating scale rules. However, in evaluation of a rating scale with visual components, such as the PANSS, video-audio recording permits a more thorough assessment which is reflected in higher inter-rater reliability between site and independent raters.

### **T53. PATIENT SELECTION FOR LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTIC USE IN SCHIZOPHRENIA/SCHIZOAFFECTIVE DISORDER: AN EXPERT CONSENSUS SURVEY**

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**Abstract:** Background: Despite availability of an increased number of LAIs, evidence-based schizophrenia guidelines provide limited recommendations concerning appropriate patients for LAI treatment (e.g., patients with frequent relapses or who prefer an LAI).

Objective: To systematically assess expert opinion on the most appropriate types of patients with schizophrenia/schizoaffective disorder for treatment with an LAI.

Methods: A panel of 34 experts (81% of solicited survey respondents) completed a 50 question survey rating the appropriateness of LAIs in relation to patient- and treatment-related characteristics. Respondents received an honorarium and were blinded to the project sponsor. The survey assessed LAI recommendations with respect to: 1) appropriate patients; 2) initiating treatment; and 3) continuation/maintenance treatment. Responses were scored on a 9-point Likert scale. Chi-square distributions across 3 ranges (1–3, 4–6, 7–9) were used to characterize expert agreement. Confidence intervals of the mean ratings designated first-, second-, or third-line categorical ratings, with a lower limit boundary  $>6.5$  for first line consensus. We describe expert recommendations on patient- and treatment-related factors most appropriate for LAI treatment.

Results: Good consensus was achieved concerning the types of patients for whom LAIs are most appropriate. When asked about patient factors relevant to LAI use, experts considered an LAI a very appropriate first-line treatment for patients with schizophrenia/schizoaffective disorder with poor insight, a history of violence, or a previous suicide attempt, as well as those who are homeless/in unstable housing, live alone, or have had >2 hospitalizations for psychotic relapse. First-line ratings did not differ based on time since onset of illness except that, for patients treated with an antipsychotic for  $\geq 2$  years, the experts also rated LAI treatment as very appropriate for young adults (18-25 years of age) and those with a substance use disorder or cognitive impairment.

When asked about treatment-related factors relevant to LAI use, experts considered an LAI a very appropriate (first-line) treatment for patients who prefer LAIs, have done well on an LAI in the past, experience family conflict related to adherence to oral medication, frequently miss clinic appointments, or whose family or care partner does not support their antipsychotic treatment regimen, as well as for patients with whom the clinician has a good therapeutic alliance.

Conclusions: This expert consensus survey identified a number of patient-related and previous treatment-related factors as important in selecting the most appropriate patients with schizophrenia/schizoaffective disorder for LAI treatment. The experts' recommendations are consistent with research findings concerning characteristics associated with medication adherence problems.

Disclosure: Work was funded by Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S.

#### **T54. OFF-HOURS USE OF A SMARTPHONE APPLICATION IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS FOLLOWING HOSPITAL DISCHARGE**

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**Abstract:** Introduction: A promise of technology-delivered healthcare interventions is that they can enhance dissemination of evidence-based treatments in areas where health literacy is low and access to specialized care is limited (Kay 2011; Steinhubl 2013; Akter 2010). An intriguing feature of technology-assisted interventions is that they allow access to on-demand services, when the patient feels he or she needs them, including when the clinic is closed. It is hypothesized that this 'just-in-time' intervention could provide tangible therapeutic benefit to patients when direct contact with clinicians is difficult or impossible. Patients with schizophrenia have been shown to be both interested in and capable of engaging successfully with technological aids (Baumel 2016; Ben-Zeev 2016).

Methods: We carried out a large, multicenter, longitudinal study of 4 technology-assisted interventions involving patients with schizophrenia spectrum disorders within 60 days of



discharge from the psychiatric hospital, a period of elevated risk for relapse and rehospitalization (Weiden 1997). The Health Technology Program (HTP) provided a multicomponent relapse prevention plan including both clinician-delivered and technology-assisted elements. For a complete description of the intervention, please see Brunette, et al, 2016. One of the technology-assisted interventions was a smartphone application called ‘FOCUS,’ which provided patients with access to evidence-based illness management strategies that could be: 1) preprogrammed by the patient and mental health technology coach (MHTC) (Mohr 2011; Ben-Zeev 2015) to ‘prompt’ use up to 3 set times per day, or 2) ‘self-initiated’ by the patient on-demand when he/she felt the need for help. FOCUS provided guidance to patients in 5 content areas: medications, mood, social, sleep and voices. For a detailed description of the development of FOCUS, please see Ben-Zeev 2013, 2014.

**Data Analysis:** This descriptive analysis centers on the self-initiated use of FOCUS outside of usual business hours. Each time a subject accessed FOCUS, the date and time-stamped login was recorded and coded as occurring: 1) during ‘normal clinic hours’ or 2) ‘off-hours.’ ‘Normal clinic hours’ were defined as 8AM-5PM, Mon-Fri, excluding weekends and bank holidays, in the local time zone where the patient was treated. ‘Off-hours’ were defined as 5PM-8AM, Mon-Fri, or any time on weekends or holidays.

**Results:** 368 patients from 10 sites enrolled in the study, of which 356 had any FOCUS usage during the 7-month study period. Of the 356 subjects with any FOCUS usage, 3 were considered screen fails, 3 declined FOCUS use, and 3 had <1 month opportunity to use FOCUS due to study closure, leaving 347 for analysis. There were a total of 75,447 FOCUS logins among the 347 patients during the study period, of which 35,739 (47.4%) were self-initiated (vs auto-prompted) and 38,139 (50.6%) were off-hours. 18,450 of the logins during off-hours (24.5% of the total, 47.8% of the off-hours logins) were self-initiated. Of the 313 subjects who self-initiated logins during off-hours, 60.7% accessed all 5 FOCUS modules, 13.7% accessed 4 modules, 8.6% 3 modules, 8.3% 2 modules, and 8.6% 1 module.

**Conclusion:** Patients with schizophrenia spectrum disorders recently discharged from the hospital utilized a smartphone application targeted to address symptom management frequently (75,447 times) during the 6-month study period. 47.4% of the logins were self-initiated, and 24.5% were self-initiated off-hours, indicating patients were possibly seeking additional help for residual symptoms when the clinic was closed. Smartphone applications may function as a useful adjunctive support for patients with schizophrenia.

## **T55. SHOULD ANTIPSYCHOTIC MEDICATIONS FOR SCHIZOPHRENIA BE GIVEN FOR A LIFETIME? A NATURALISTIC FOLLOW-UP STUDY**

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**Abstract:** Antipsychotic medication has been the treatment of choice for schizophrenia for many decades. What has not been clear – since a double blind randomized controlled trial is not feasible– is how long after the initial episode or onset of antipsychotic treatment to continue medication to achieve the best outcome. We designed a small, clinical study to retrospectively examine medication adherence and outcome. This is a naturalistic study of 35 patients with chronic schizophrenia examining antipsychotic medication adherence from 8-50, average 21 years after onset of antipsychotic treatment. The sample was derived from all patients in one physician’s academic clinic. Information was gathered on medication adherence, long-term global outcomes (based on both patient ratings as well as a blind-clinician’s assessment on both

a Global Outcome Scale and the Global Assessment of Function scale), and the patient-rated Satisfaction with Life Scale. Spearman's rank order correlations were used to relate medication adherence to global outcomes and life satisfaction, as were linear regression models adjusted for demographic and clinical characteristics. A total of 35 patients, mean age 45, and mean 21 years of possible medication since onset of treatment were assessed. Medication adherence was a statistically significant predictor of better long-term global outcomes and life satisfaction, both in Spearman's rank order correlations and in covariate-adjusted linear regressions (all p-values <0.01). Poor medication adherence was associated with poor outcomes, often disastrous, with low life satisfaction. Other variables did not explain the difference between those who adhered and those who didn't.

## **T56. PROGNOSIS OF PATIENTS WITH SCHIZOPHRENIA TREATED WITH ANTIPSYCHOTIC COMBINATIONS: A SECONDARY ANALYSIS OF PROACTIVE DATA**

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**Abstract:** Background: Combination antipsychotics are prescribed in 10-30% cases of schizophrenia despite of risks and limited evidence of efficacy. We performed a secondary analysis on PROACTIVE study data in which 305 patients with schizophrenia and schizoaffective disorder were followed for 30 months after randomization to long acting injectable (LAI) risperidone or oral 2nd generation antipsychotic (OA) to explore the effect of switching to antipsychotic monotherapy on patients who entered the study on combination of antipsychotics (CA).

Methods: Study participants were classified into three groups based on their antipsychotic medication status at study entry: LAI (n = 20), single OA (n = 206), and CA (n = 50). The groups were compared in terms of each of Brief Psychiatric Rating Scale (BPRS) clinical measures: anxiety-depression, activation-excitement, psychosis cluster, anergia-negative symptoms and total score; the Scale of Function; number of prior hospitalizations and time to relapse. To account for baseline differences between groups, "change scores" were calculated for each clinical measure for each subject. We then compared the three groups in terms of improvement in the clinical measures over the course of the study, controlling for randomized treatment assignment. The chi-square test was used to compare the three groups in terms of the percentage in each group who suffered a relapse. The Kaplan-Meier method was used to construct survival curves for time until first relapse in the three groups and the log-rank test was used to compare the groups in terms of overall "survival."

Results: There was a significant difference among the three groups of patients on number of hospitalizations prior to baseline ( $9.8 \pm 22$  for LAI,  $8.6 \pm 14$  for OA and  $11.4 \pm 11.6$  for CA,  $p = 0.011$ ); the CA group had significantly more hospitalizations than the OA group ( $p = 0.009$ ). There were significant differences among the three groups on BPRS total score at endpoint ( $p = 0.002$ ); the CA group ( $37.5 \pm 9.4$ ) had a significantly greater (more severely ill) score than the OA group ( $32.2 \pm 9.1$ ,  $p = 0.003$ ). Other differences between groups at baseline and endpoint were noted in BPRS anxiety-depression, psychosis cluster and anergia. The log-rank test indicated a significant difference among the three groups in terms of time to first relapse ( $\chi^2 = 6.81$ , d.f. = 2,  $p = 0.033$ ); the time to relapse was significantly shorter in the CA group (mean 409.5, median 252.0 days) than in the single OA group (mean 562.8, median 772.0 days,

p = 0.011). The LAI group did not differ significantly from either of the other groups in time to first relapse (mean 594.0, median 827.0 days).

Conclusions: There was a significant difference in subjects' number of hospitalizations prior to baseline, with the highest number in the CA group. There was a striking difference in time to first relapse for subjects on combination antipsychotics vs. those on oral and those on LAI at baseline. Our results validate clinical decision making that led treating physicians to use combination antipsychotics. Our rating scales detected greater illness severity at study end point but not at study entry in those who received CA. Our analysis confirms the clinical guidance that being on two antipsychotics and having more hospitalizations is an indicator of greater risk and predicts earlier relapse in schizophrenia. Further treatment guidance is needed for this group of patients, since treatment with oral or LAI antipsychotic monotherapy does not improve their risk of relapse.

### **T57. EFFECTS OF ONCE-DAILY VALBENZAZINE ON TARDIVE DYSKINESIA BY BODY REGION: SHIFT ANALYSES OF KINECT 3 STUDY DATA**

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**Abstract:** Background: Valbenazine (VBZ, NBI-98854) is a novel, highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor that has been evaluated for the treatment of tardive dyskinesia (TD) in several randomized, double-blind, placebo (PBO)-controlled trials. Since the distribution and severity of TD can be heterogeneous, Abnormal Involuntary Movement Scale (AIMS) data from a Phase 3 clinical trial (KINECT, NCT02274558) were analyzed to explore the effects of valbenazine on TD in different body regions.

Methods: In KINECT 3, adults with TD were randomized (1:1:1) to once-daily VBZ 80 mg, VBZ 40 mg, or PBO. The primary efficacy endpoint was the mean change from baseline to Week 6 in the AIMS dyskinesia total score (80 mg vs PBO). Shift analyses were conducted for each of the 7 individual AIMS items that constitute the dyskinesia total score. Shifts were defined as the percentage of subjects who improved from a moderate/severe rating (item score  $\geq 3$ ) at baseline to a mild/minimal/none rating (item score  $\leq 2$ ) at Week 6. The percent of subjects with a shift in  $\geq 2$  body regions (AIMS items) was also analyzed. Analyses were conducted in subjects with an available AIMS assessment at baseline and Week 6 (80 mg, n=70; 40 mg, n=63; PBO, n=69).

Results: The numbers of subjects with an AIMS item score  $\geq 3$  at baseline were: face (n=16), lips/perioral (n=36), jaw (n=60), tongue (n=57), upper extremities (n=15), lower extremities (n=14), neck/shoulders/hips (n=28). The percentage of subjects by treatment group who met the shift criteria for each body region were as follows (VBZ 80 mg, VBZ 40 mg, PBO): face (2.9%, 3.2%, 1.4%), lips/perioral (17.1%, 12.7%, 8.7%), jaw (17.1%, 27.0%, 15.9%), tongue (15.7%, 17.5%, 4.3%); upper extremities (5.7%, 3.2%, 7.2%); lower extremities (10.0%, 3.2%, 2.9%); neck/shoulders/hips (8.6%, 12.7%, 2.9%). The percentage of subjects with shifts in  $\geq 2$  body regions was 18.6%, 22.2%, and 8.7% for VBZ 80 mg, VBZ 40 mg, and PBO, respectively.

Conclusions: In subjects with scores  $\geq 3$  in individual AIMS items at baseline, both doses of valbenazine (80 and 40 mg/day) were associated with greater TD improvement relative to

placebo in 6 out of 7 body regions. While the primary outcome (i.e., AIMS dyskinesia total mean score change from baseline) documents efficacy of valbenazine in a group of subjects, these shift analyses may be more appropriate for understanding individual patient responses.

**T58. RESULTS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED, TOLERABILITY STUDY OF KARXT: A NOVEL COMBINATION TARGETING MUSCARINIC ACETYLCHOLINE RECEPTORS USING XANOMELINE WITH TROSPIUM CHLORIDE TO MITIGATE CHOLINERGIC SIDE EFFECTS**

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**Abstract:** Background: Muscarinic receptors, particularly M1 and M4, have long been of therapeutic interest for the treatment of psychosis and cognitive impairment. Xanomeline is a preferential M1 /M4 agonist that in both schizophrenia and Alzheimer's disease has demonstrated efficacy for psychosis, and generated promising data for treating cognitive impairment. However, xanomeline produces peripheral cholinergic side effects (nausea, vomiting, diarrhea, excess sweating and salivation) that led to the discontinuation of its development. KarXT is a novel therapeutic in development which combines xanomeline with trospium chloride, a muscarinic antagonist which does not cross the blood-brain barrier, to mitigate peripheral muscarinic effects to improve the tolerability of xanomeline while maintaining its efficacy profile.

Methods: 70 healthy volunteers participated in a double-blind, parallel group, randomized (1:1) trial of trospium chloride 20 mg BID or placebo added to xanomeline 75 mg TID. The objective of the study was to determine if KarXT produced improved tolerability compared to xanomeline plus placebo. There was a two-day run-in period when subjects received only placebo or trospium followed by 7 days of xanomeline in addition to placebo or trospium. Safety and tolerability were analyzed using spontaneous reports of adverse events including five pre-specified cholinergic adverse events (nausea, vomiting, diarrhea, excessive sweating and salivation), visual analog scales (VAS), and clinician-rated measures.

Results: KarXT (trospium plus xanomeline), as compared to placebo plus xanomeline, reduced the incidence of all spontaneously reported cholinergic adverse events: 34.3% vs. 63.6%,  $p=0.016$ , respectively. Spontaneous reports of each individual cholinergic adverse event were as follows for KarXT vs placebo plus xanomeline, respectively: nausea (17.1% vs 24.2%), vomiting (5.7% vs 15.2%), diarrhea (5.7% vs 21.2%), excess sweating (20.0% vs 48.5%), and excess salivation (25.7% vs 36.4%). KarXT was well tolerated with no associated serious AE's. During the run-in period, 32% of subjects receiving only placebo reported at least one cholinergic adverse event.

KarXT, as compared to placebo plus xanomeline, had lower mean weekly maximum composite cholinergic VAS scores (2.29 vs. 3.82,  $p=0.30$ , respectively). Mean VAS scores for individual cholinergic symptoms were consistently lower in the KarXT group. However, due to low self-reported scores on the VAS scales, these measures were not sufficiently sensitive to detect statistical differences between groups.

On the clinician-rated Postoperative Nausea and Vomiting Scale, nausea and vomiting were seen less frequently in the KarXT group compared to the placebo + xanomeline group (14.7% and 2.9% vs. 25.0% and 15.6% respectively). Using the Unified Parkinson's Disease Rating Scale, excess salivation was seen less frequently in the KarXT group (3.2% vs. 16.1%). On

the Hyperhidrosis Disease Severity Scale, excess sweating was less common in the KarXT group (3.2% vs. 19.4%).

Conclusions: This KarXT proof-of-concept tolerability study demonstrates that the addition of trospium chloride results in a clinically meaningful improvement in the tolerability of xanomeline. The results described here together with previous efficacy data in schizophrenia and Alzheimer's disease suggests the potential therapeutic utility of KarXT as a novel antipsychotic and procognitive agent. A Phase II, inpatient, double-blind, placebo-controlled, monotherapy trial of KarXT in schizophrenia patients with an acute exacerbation of symptoms is planned.

## **T59. MEAN SQUARE SUCCESSIVE DIFFERENCE AS A MARKER OF DATA QUALITY IN SCHIZOPHRENIA TRIALS - EXPLORATORY ANALYSIS**

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*Bracket Global, LLC*

**Abstract:** Introduction: We have previously identified a number of markers of rater and subject behavior that predict subsequent data quality (Kott et al, 2016). While these indicators are extremely powerful in identifying data concerns at visit level, their utility in identifying accumulation of unusual score patterns in the data at the level of the site is limited. Mean Square Successive Difference (MSSD) is a measure of temporal instability based on variability and temporal dependency over time (Jahng et al, 2008). The objective of this exploratory analysis was to evaluate the utility of MSSD and a risk indicator in identifying research sites with scoring patterns significantly different from the overall study data.

Methods: Data from 17 phase 2 and phase 3 double blind, placebo controlled schizophrenia studies were analyzed. For each subject in the database we calculated the PANSS mean square successive difference (MSSD) and within each study identified subjects with their MSSD either below 5th or above 95th percentile as subjects with low or high MSSD, respectively. Outlying sites were identified using logistic regression as sites with significantly increased odds of having subjects with either low or high MSSD, respectively.

Results: The dataset consisted of 97,016 collected visits across 11,487 subjects at 1,323 research sites. The median MSSD was 23.6 in the overall dataset, with differences between acute and maintenance studies (median approx. 40) and negative and non-negative non-acute studies (median approx. 14.5). Using logistic regression, we identified 120 (9%) sites with significantly increased odds of presence of patterns characterized by low MSSD (unusual temporal stability) and 147 (11%) sites with significantly increased odds of presence of patterns characterized by high MSSD (unusual temporal instability).

Conclusions: Significant heterogeneity exists in the patterns of symptom change across subjects participating in schizophrenia clinical trials. Accumulation of subjects with specific patterns at a research site may be indicative of potential data quality issues in areas such as interviewing or rating methodology, subject selection, etc. Where possible, identified sites should be investigated by review of recorded interviews, worksheets, etc., and remediated if appropriate. We have demonstrated the utility of calculating the mean square successive differences to identify a subgroup of sites with significantly increased odds of unusual scoring patterns. We further plan to validate this indicator in analysis of unblinded datasets.

## **T60. PANSS AND CGI-S: 10-YEARS LATER A FURTHER EXAMINATION OF THEIR RELATIONSHIP**

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**Abstract:** PANSS and CGI-S: 10-Years Later a Further Examination of their Relationship

**Objective:** The Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) scale are frequently used as endpoints in schizophrenia clinical trials. The level of agreement between these two scales and clinical meaningfulness of the PANSS in relation to the CGI has been reported in the literature (e.g., Leucht, 2005). The present study aimed to replicate and expand upon on this work using a large dataset spanning multiple trials, and examine the level of association when both measures are administered by the same rater in clinical trials.

**Methods:** Aggregated data from 7 clinical trials of schizophrenia that administered both the PANSS and CGI-S were reviewed (n= 2,965, with a total of 12,476 PANSS/CGI assessments). Both scales were administered by a cohort of expert calibrated clinicians. The correspondence of PANSS total score with CGI severity score was tested against established criteria (Leucht, et al., 2005), and the correlation between them was also examined.

**Results:** Pooled study means for the PANSS total and CGI-S scores were 81.5. (SD=16) and 4.3 (SD =0.9), respectively. This corresponds to a ‘moderately’-to-‘markedly ill’ aggregate population using criteria from Leucht et al., 2005. The mean PANSS total scores at each of the seven CGI severity stages were of 37.1, 47.2, 60.1, 77.1, 93.3, 108.5, and 136.3, respectively, which all fell within range of Leucht et al.’s findings. There was a strong and significant correlation between PANSS total and CGI-S scores ( $r = .91$ ,  $p < .0001$ ); the Pearson correlation coefficients for the studies within the cohort ranged from .80 to .92, all significant. Of 12,476 PANSS-CGI scores, 1,159 (9%) were flagged as misaligned, according to Leucht and colleague’s criteria.

**Conclusion:** The present study utilized a large dataset spanning multiple schizophrenia studies, and provides additional evidence for the substantial agreement between PANSS total score and CGI-S rating when administered by the same central rater as originally reported by Leucht and colleagues. However, this study had a higher overall correlation ( $r = 0.91$ ) versus ( $r = 0.56$ -to- $0.73$ ) that is likely attributable to implementation of calibrated central clinicians. Overall, this study found significant shared variance between these scales (i.e., 83%), which raises questions concerning the additional value of the CGI-S, especially considering this measure’s known expectancy bias (when given following the PANSS) and psychometric limitations (Leucht et al., 2005).

## **T61. POPULATION PHARMACOKINETIC ANALYSIS AND SIMULATIONS OF A 2-MONTH REGIMEN FOR ARIPIPRAZOLE LAUROXIL**

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**Abstract:** Background: Aripiprazole lauroxil (AL) is a prodrug of aripiprazole, formulated as an extended-release suspension approved for the treatment of schizophrenia by injection every 4 and 6 weeks. Because of the clinical need to expand the range of dose interval options, a

Phase 1 study was conducted to evaluate an every-8-week (i.e., 2-month) AL regimen. The pharmacokinetic (PK) data were subsequently used to develop a PK model that was used to further evaluate its potential for clinical use as a 2-month dose option.

**Methods:** An existing population pharmacokinetic (PopPK) model of AL was updated to include data from 5 clinical studies, including a recently completed Phase 1, open-label study evaluating the PK of AL after administration of 441, 882 or 1064 mg at 4-, 6-, and 8-week intervals in n=139 subjects with stable schizophrenia. The results of this study were combined with data from 4 prior clinical PK studies (n=561) for the analysis. The final PopPK model was subsequently used to assess the exposure of the 8-week regimen relative to already approved AL regimens (441, 662 and 882 mg monthly, and 882 mg every 6 weeks), the impact of missed doses, and re-initiation of treatment with AL 1064 mg every 8 weeks following a delay in dosing.

**Results:** As determined in the clinical study and through model-based simulations, repeated administration of AL 1064 mg every 8 weeks resulted in aripiprazole concentrations within the aripiprazole exposure range associated with the efficacious dose range of AL. Additionally, median simulated steady-state concentrations of aripiprazole for the 8-week regimen were comparable to the 882 mg every 6 weeks and 662 mg monthly regimens (154 ng/mL, 165 ng/mL and 183 ng/mL, respectively). Aripiprazole concentrations declined slowly when a dose was delayed, declining by <20% for a 14-day delay of the 8-week regimen, and readily returned to expected levels when AL dosing was resumed.

**Conclusion:** A higher dose of AL (1064 mg) resulted in aripiprazole concentrations that support extending the AL dose interval. The 1064 mg every-8-week regimen resulted in aripiprazole concentrations within the aripiprazole concentration range of the lowest and highest therapeutic doses of the currently available AL monthly regimens. These results show that 1064 mg AL may be suitable for a 2-month dose interval, having the potential to expand the choice of AL treatments.

## **T62. SAFETY AND TOLERABILITY OF 4, 6 AND 8 WEEK DOSE INTERVALS OF LONG-ACTING ARIPIPRAZOLE LAUROXIL**

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**Abstract:** Introduction: Extending the dose intervals available for long-acting atypical injectable antipsychotics will offer greater options for clinicians and patients to choose a specific dose and interval that is best for the individual's treatment plan. Aripiprazole lauroxil (AL) is an FDA-approved treatment for schizophrenia. This Phase 1 study evaluated the pharmacokinetics (PK) and safety of a new AL dose (1064mg) developed to extend the dose interval beyond the currently approved 4- and 6- week injection intervals. The study assessed the pharmacokinetics and safety of the 1064mg/8-week regimen using a randomized open-label, parallel design. The two other dose/ interval groups were 882mg q6-weeks and 441mg q4-weeks.

**Methods:** A total of 139 patients with a diagnosis of schizophrenia already stabilized on a first-line antipsychotic (other than aripiprazole) were randomized 1:1:1:1 into 1 of 4 dose/interval groups: a 4-week interval of AL 441mg (n=35), a 6-week interval of AL 882mg (n=34) and either 1 of 2 different formulations of AL 1064mg dosed at 8-week intervals (combined n=70). Patients continued on their prior antipsychotic throughout. After randomization, AL

assignment was open-label and administered as gluteal intramuscular injections over 24 weeks. Patients were followed every 2 weeks and the open-label injections occurred at the respective dose intervals. Injection number was related to the interval: 4 injections for the 1064mg/8-week group, 5 for the 882mg/6-week, and 7 for the 441mg/4-week groups, respectively. Safety assessments occurred every 2 weeks and extended for an additional 20 weeks after the last injection.

**Results:** As the outcomes for subjects that received either formulation of AL 1064mg were similar, they were combined into a single AL 1064mg group. Administration of AL 1064mg every 8 weeks provided continuous exposure to aripiprazole roughly comparable to the 882mg q6-weeks AL dose (further details in companion presentation). The overall safety profile of the group randomized to the 1064mg/8-week combination was comparable to the 6-week/882mg and 4-week/441mg groups. The most common adverse event (AE) for all groups was injection-site pain which ranged from 8.6%–11.4% across the dose/interval groups. There was no apparent dose-AE relationship for extrapyramidal symptoms, akathisia, sedation or weight gain.

**Conclusion:** The aripiprazole lauroxil formulation provides for a sustained release of aripiprazole with an extended pharmacokinetic profile, and provides the option for a range of dose/interval combinations. In this study, the safety of each dose/interval tested was similar; no pattern of dose- or interval-related safety findings was evident. Limitations include small sample size, lack of a placebo-arm and continued co-prescribing of another oral antipsychotic. However, there did not seem to be any major safety problems from the exposure to another oral antipsychotic alongside the AL therapy. The results of this study show that the safety and tolerability of the 1064mg/8-week AL may be suitable as a 2-month dose interval option. This study was funded by Alkermes, Inc.

### **T63. LONG-TERM SAFETY OF ARIPIPRAZOLE LAUROXIL FOR MAINTENANCE TREATMENT OF SCHIZOPHRENIA**

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**Abstract:** Background: Aripiprazole lauroxil (AL) is approved for the treatment of schizophrenia. Given the long-term nature of schizophrenia treatment, having safety information commensurate with treatment duration is important. The focus of this analysis is on safety and tolerability issues associated with starting and continued long-term treatment with aripiprazole lauroxil over one year.

**Methods:** Patients were enrolled in the first of two consecutive long-term safety studies of AL given as either 441mg or 882mg every 4 weeks for maintenance treatment over a year (N=478). To assess timing of when certain adverse events (AEs) arise, 3 post hoc categories were established according to AL and injection exposure at the safety study baseline. Group 1 ("de novo"; n=242) started AL as they entered the study and received their first 882mg AL injection with 3 weeks of oral aripiprazole, and 882mg q4wks thereafter. Group 2 ("active rollover"; n=181) entered after 12 weeks (3 injections) of active AL (either 441mg or 882mg) and continued the same AL dose (remaining double-blind) with a fourth injection (+ 3 weeks of oral placebo [PBO]). Group 3 ("placebo rollover" n=55) entered after 12 weeks but having



received 3 injections of PBO. Upon entering the safety study, this group's fourth injection now was active AL (+ 3 weeks of active oral). All the safety analysis baseline values were obtained from the visit with the first active AL injection. Patients were followed for a year or until discontinuation. Movement disorders (akathisia and Parkinsonism) were assessed by AEs timing along with rating scales. Timing of AE onset compared "de novo" and both "rollover" groups to determine the degree to which some AEs (e.g. injection site reactions [ISRs], akathisia) are based by number of injections given or time exposed to aripiprazole, respectively. Changes in metabolic parameters and serum prolactin were assessed over the duration of AL exposure.

#### Results:

1. More than two thirds of subjects completed the year, and retention rates did not differ by maintenance dose (68% for 441mg and 69% for 882mg patients).
2. ISRs were highest in Group 1 "de novo" patients (8.3%) compared to Group 2 "active rollover" of 1.3%, and were not observed in the "placebo rollover" group.
3. Akathisia was higher among "de novo" (4.1%) than "active rollover" patients (who already finished 12 weeks of AL (1.65%). Most of the akathisia AEs occurred within 3 months (15 out of 478; 3.1%) with only 4 other akathisia AEs reported for rest of the year. In the placebo rollover group, the rate was (3/55; 5.5%).
4. Parkinsonism as an AE was more common for the patients maintained with 882mg (4.9%) than those receiving 441mg (2.7%).
5. Long-term weight changes were modest with a mean increase in body weight of 0.8kg from baseline to last assessment).
6. Long-term metabolic changes were also modest, with mean change of +1.1 mg/dL for glucose, -3.3 mg/dL for total cholesterol and -5.3 mg/dL for triglycerides. There did not appear to be any relationship between dose and any of these parameters.
7. Prolactin change from baseline (prior to first AL injection) and last visit was -8.7ng/mL for men and -14.9ng/mL for women.

Conclusions: This is the first comprehensive report of the long-term safety of AL for maintenance treatment of schizophrenia. These findings provide important information about the relative timing and frequency of safety and tolerability concerns that can better inform clinical practice.

## **T64. EVALUATION OF THE POTENTIAL FOR VALBENZAZINE TO ELICIT DRUG INTERACTIONS**

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**Abstract:** Background: Valbenazine (VBZ) is a vesicular monoamine transporter 2 (VMAT2) inhibitor in development for the treatment of tardive dyskinesia. The potential for VBZ to affect the pharmacokinetics (PK) of concomitant medications was assessed through in vitro and clinical studies.

Methods: In vitro studies evaluated potential inhibition and induction of common cytochrome P450 (CYP) drug metabolizing enzymes and inhibition of drug transporters by VBZ and its active metabolite, NBI-98782. CYP inhibition was assessed by incubating VBZ and NBI-98782 with human liver microsomes and measuring CYP1A2, CYP2B6, CYP2C8, CYP2C9,

CYP2C19, CYP2D6, CYP2E1, and CYP3A4 activity. CYP induction was evaluated in fresh primary-cultured hepatocytes by measuring CYP1A2, CYP2B6 and CYP3A4/5 activity following incubation with VBZ and NBI-98782 for 3 days. Drug transporter inhibition was assessed by incubating VBZ and NBI-98782 in cell systems expressing OAT1, OAT3, OCT2, OATP1B1, OATP1B3, BCRP or P-glycoprotein (P-gp) transporters and measuring transporter activity. Single-center, open-label clinical studies evaluated the potential for VBZ to affect the PK of midazolam (MID), a sensitive CYP3A4 substrate, and digoxin (DIG), a sensitive P-gp substrate. In one study, 24 healthy male (N=12) and female (N=12) subjects received DIG 0.5 mg with (Test) or without (Reference) concomitant VBZ 80 mg once-daily (QD) for 7 days. In the second study, 12 healthy male (N=6) and female (N=6) subjects received MID 2.0 mg with (Test) or without (Reference) a concomitant single VBZ 80 mg dose. Plasma concentrations were determined through 48 h post-dose for MID and 72 h post-dose for DIG. PK parameters were determined using standard non-compartmental methods. Statistical analyses were conducted by determining the point estimate and two-sided 90% confidence interval (CI) for Test to Reference (T/R) differences of log-normalized PK parameters.

Results: VBZ and NBI-98782 were weak direct inhibitors of CYP2D6 (IC<sub>50</sub>: 3760 and 4470 ng/mL, respectively). These IC<sub>50</sub> values exceed typical peak clinical exposures at 80 mg QD, suggesting a low potential for a clinically-relevant interaction. All other IC<sub>50</sub> values were greater than 9600 ng/mL. There was no observed time-dependent inhibition of CYP enzymes by VBZ or NBI-98782. At concentrations up to 3200 ng/mL, neither VBZ nor NBI-98782 induced CYP enzyme activity. VBZ weakly inhibited P-gp transport (IC<sub>50</sub>: 9950 ng/mL). No other clinically-relevant effect of VBZ or NBI-98782 on drug transporter activity was observed. In the DIG study, T/R ratios of DIG C<sub>max</sub> and AUC<sub>inf</sub> were 192% (90%CI: 166-221%) and 136% (90%CI: 126-148%), respectively. Mean DIG t<sub>1/2</sub> was similar with (35 h) or without (36 h) VBZ, suggesting that VBZ increases the extent of DIG absorption, but does not affect the elimination of DIG. This hypothesis is consistent with VBZ concentrations after oral administration being higher in the gastrointestinal tract during absorption than in the systemic circulation. In the MID study, T/R ratios of MID C<sub>max</sub> and AUC<sub>inf</sub> were 102% (90%CI: 86-121%) and 107% (90%CI: 100-114%), respectively, indicating that VBZ did not affect the PK of MID.

Conclusions: Overall, these data indicate that VBZ has minimal potential to affect the CYP-mediated metabolism of concomitant medications. Also, with the exception of potential increased absorption of sensitive P-gp substrates, VBZ has a low potential to affect the PK of co-medications that are drug transporter substrates.

## **T65. BREMELANOTIDE (BMT) FOR HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD): EFFICACY ANALYSES FROM THE RECONNECT STUDY**

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**Abstract:** Background: The most common sexual concern expressed by women is diminished or lack of desire for sexual activity. When accompanied by distress this may be diagnosed as HSDD. BMT's mechanism of action is different from the only approved treatment for HSDD, thus providing an important option.

**Objective:** The objective of the RECONNECT Study was to evaluate the efficacy of BMT as a treatment for HSDD in premenopausal women.

**Material/Method:** The RECONNECT study comprises 2 Phase 3, multicenter trials (301, 302) consisting of a 4-week screening period; a Core Phase (4-week at-home placebo period to establish baseline followed by a 24-week randomized, double-blind treatment period); and an ongoing 52 week open-label extension. During the Core Phase participants self-administered BMT (1.75 mg) or placebo subcutaneously using an auto-injector, as-desired, prior to sexual activity. The co-primary endpoints were change in the desire domain of the Female Sexual Function Index (FSFI-D) and the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) score for feeling bothered by low sexual desire (Item 13). Secondary endpoints were change from baseline to end-of-study in the FSFI total, arousal, lubrication, orgasm, and satisfaction scores; FSDS total and bother scores; Women's Index of Treatment Satisfaction (WITS-9) score; self-assessment of benefit, and satisfying sexual event (SSE) items of the Female Sexual Encounter Profile-Revised (FSEP-R).

**Results:** The primary efficacy population (Modified Intent-to-Treat) comprises 1202 participants; 856 of whom completed the double-blind phase. Participants were: mean age 39 years, mostly white (>80%), with a mean BMI of 28.7 kg/m<sup>2</sup>. The most frequent diagnosis was HSDD with decreased arousal. Both studies met the pre-specified co-primary efficacy endpoints with clinically meaningful results. Compared with those taking placebo, women using BMT had significantly increased scores on the FSFI-D (Study 301: mean change 0.54 vs 0.24; P=0.0002; Study 302: mean change 0.63 vs 0.21; P<0.001) indicating an increase in desire. Scores for item 13 of the FSDS-DAO showed a significant reduction in distress related to low sexual desire for women using BMT compared to placebo (Study 301: Mean change -0.74 vs -0.35; P<0.0001; Study 302: Mean change -0.71 vs -0.42; P=0.0057). On the secondary outcomes, BMT was associated with significant improvements from baseline to EOS in FSFI total, arousal, lubrication, orgasm, and satisfaction domain scores (all P≤0.01), FSDS total and bother scores (both P≤0.01), and WITS-9 and self-assessed benefit (both P<0.0001). FSEP-R scores for satisfaction with desire and arousal were significantly improved in Study 301 (P≤0.01) but only trending toward significance in Study 302. Changes in the number of SSEs were not significantly different from placebo in either study; however, women taking BMT reported a higher percentage of sexual encounters as satisfactory (64.4% vs 50.9% in Study 301 and 64.8% vs 47.3% in Study 302). The most frequent adverse events were nausea, flushing, and headache; most were mild or moderate. BMT's safety profile was consistent with prior experience.

**Conclusions:** Treatment with BMT is associated with clinically meaningful and statistically significant improvement in desire and a decrease in distress; both hallmark characteristics of HSDD. BMT is an efficacious treatment for key aspects of sexual function — desire, arousal, lubrication, and orgasm, in premenopausal women.

#### **T66. A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF SAGE-547 INJECTION IN THE TREATMENT OF SEVERE POSTPARTUM DEPRESSION**

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**Abstract:** Background: Postpartum depression (PPD) affects an estimated 10-15% of new mothers and can lead to significant morbidity and mortality for both mother and infant, yet there are no medications specifically indicated for PPD. It has been suggested that changes in the mother's hormone levels, such as the precipitous drop in allopregnanolone following delivery, may play a role. An earlier proof-of-concept, open-label study in 4 women with severe PPD showed favorable tolerability and improvements in efficacy measures following infusion of SAGE-547 Injection, a proprietary, soluble formulation of allopregnanolone. Those results supported further investigation of SAGE-547 Injection in patients with PPD.

Methods: This Phase 2, double-blind, placebo-controlled study enrolled 21 women with severe PPD, defined by a 17-item Hamilton Rating Scale for Depression (HAM-D) total score of  $\geq 26$ . Subjects had a major depressive episode that began no earlier than the 3rd trimester and no later than the first 4 weeks following delivery and were  $\leq 6$  months postpartum at enrollment. Subjects were randomized 1:1 for 60-hour (hr) IV infusions of SAGE-547 Injection (n=10) or placebo (n=11). The primary endpoint was change from baseline in HAM-D total score at 60 hrs compared with placebo. Adverse events (AEs) were also assessed.

Results: The primary efficacy endpoint was achieved; subjects receiving SAGE-547 Injection showed a statistically significant reduction in HAM-D total score at 60 hrs (p=0.008) compared with those receiving placebo. This treatment difference began at 24 hrs (p=0.006) and was maintained through the 30-day follow-up (p=0.01). Remission from depression (HAM-D  $\leq 7$ ) was also statistically significant versus the placebo-treated group at 24 (p=0.024), 48 (p=0.030), 60 (p=0.008), and 72 (p=0.030) hrs and at Days 7 (p=0.003) and 30 (p=0.030). At the primary time point (60 hours post infusion start), 70% of SAGE-547 Injection subjects vs. 9% of placebo subjects achieved remission. SAGE-547 Injection was generally well tolerated, with no deaths, serious AEs, or discontinuations due to AEs. 8 placebo-treated and 4 SAGE-547-treated patients had at least one AE. There were 3 patients who received SAGE-547 with AEs of sedation or somnolence (all mild/moderate) vs. none with placebo.

Conclusions: In this Phase 2, double-blind, placebo-controlled study in women with severe PPD, SAGE-547 Injection treatment resulted in statistically significant and clinically meaningful reductions in HAM-D total score at 24 hours with results sustained at 30 days, and was generally well tolerated. Additional pivotal studies in patients with severe and moderate PPD are ongoing.

#### **T67. DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF IMMEDIATE-RELEASE VILOXAZINE (SPN-812 IR) AS A NOVEL NON-STIMULANT THERAPY IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

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**Abstract:** Background: The goal of this study is to determine the safety and efficacy of immediate-release viloxazine (SPN-812 IR), a structurally distinct, bicyclic norepinephrine reuptake inhibitor (NRI), with antagonistic activity observed at 5-HT<sub>7</sub> and 5HT<sub>1B</sub> receptors

and agonistic activity at 5-HT<sub>2B</sub> and 5HT<sub>2C</sub> receptors, in adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: Phase 1/2a, multicenter, double-blind, randomized, placebo-controlled, proof-of-principle study at a target dose of 300 mg per day SPN-812 IR (standard dose for non-US depression indication). Starting dose of 150 mg per day for 1 week increased to 300 mg per day for 5 weeks. Efficacy measures included investigator-rated Conners' Adult ADHD Rating Scale (CAARS), Clinical Global Impression-Improvement (CGI-I), and subject self-rated CAARS.

Results: Safety and intent-to-treat (ITT) populations were used in this study (SPN-812 IR, n = 26; placebo, n = 25). Twenty-four (92%) of the randomized subjects in each group completed the study. SPN-812 IR generally was well tolerated. Most common adverse events (AEs) included the following: with SPN-812 IR, nausea (39%), decreased appetite (31%), headache (31%), insomnia (31%), and dry mouth (23%); with placebo, headache (36%) and dry mouth (12%). No serious AEs or deaths were reported. One subject discontinued SPN-812 IR because of AEs. Efficacy of treatment is indicated as follows: after 6 weeks of treatment, investigator CAARS median reduction was 11.5 points (SPN-812 IR) vs. 6.0 points (placebo, P = 0.041); and subject CAARS median reduction was 10.5 points (SPN-812 IR) vs. 1.0 point (placebo, P = 0.035). Between-group difference in median CGI-I score was not significant.

Conclusions: SPN-812 IR for 6 weeks produced significantly greater ADHD symptom reduction vs. placebo in adults. SPN-812 IR generally was well tolerated; AE profile was consistent with the established profile for immediate-release viloxazine. Results suggest that further development of an extended-release formulation is appropriate, with the aim of reducing dose frequency and altering the plasma concentration-time profile for improved tolerability.

## **T68. AN UPDATED GENETIC MODEL FOR CLOZAPINE RESPONSE**

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**Abstract:** Background: Despite its clinical utility, a pharmacogenetic test for response to clozapine (CLZ) has yet to be developed. In the past 20 years, multiple genetic variants (e.g. dopamine, serotonin) have been suggested to be associated with CLZ response. Arranz et al. (2000) proposed a model to predict response, but it was not replicated in independent samples. Since then, no other studies have sought to create a genetic panel predicting treatment response to CLZ. Thus, we reinitiated the effort to develop a genetic model for CLZ response incorporating the most promising findings from our group's repository of response studies.

Methods: Our sample consisted of 151 Caucasian subjects with schizophrenia (SCZ) (DSM-III) treated with CLZ for six months. Response was assessed using the Brief Psychiatric Rating Scale (BPRS), and evaluated using absolute score change and binary response (Kane et al. 1988 criteria), with baseline score as a covariate. A total of 99 polymorphisms were tested from a range of candidate genes. Variants showing at least a nominal statistical trend ( $p < 0.1$ ) were included in the model. An unweighted risk score was calculated for each SNP and assessed for association with response. Five-fold cross validation was performed in an attempt to limit model overfitting. The model was then tested in an independent sample of antipsychotic-treated

SCZ patients of European ancestry (CATIE subsample, N=390) to examine generalizability of findings to other antipsychotics.

Results: Four markers from genes encoding for the dopamine D2 receptor (DRD2), serotonin-6 receptor (5-HT6), brain-derived neurotrophic factor (BDNF), and neurexin-1 (NRXN1) were included in the model. We observed a statistically significant association between genetic risk score with BPRS score change ( $p=0.000039$ , Adjusted  $R^2=0.565$ ) and binary response ( $p=0.004$ , Nagelkerke  $R^2=0.097$ ) assuming a linear increase in response for each additional risk allele. The model had an accuracy of 62%, a sensitivity of 70%, and a specificity of 47%. The model was not significantly associated with response in the independent CATIE European Caucasian subsample treated with other antipsychotics ( $p=0.10$ ).

Discussion: We have developed a preliminary genetic model for CLZ response that includes genes with strong rationale for involvement. NRXN1 is a synaptic membrane cell-adhesion protein that has been suggested to modulate NMDA receptor activity, which is indirectly regulated by CLZ. The 5-HT6 receptor is involved in neurite growth and has lower expression in the hippocampus of SCZ patients compared to healthy controls. It mediates cognitive function, anxiety, and positive symptom improvement in animal models of SCZ.

The model does not appear to generalize to other antipsychotics. For clozapine response prediction per se, replication in independent studies of CLZ response in SCZ is required to confirm the validity of these findings.

We are currently employing a genome-wide approach to identify additional genetic predictors for CLZ response. These will subsequently be incorporated into the model.

## **T69. USING ARTIFICIAL INTELLIGENCE PLATFORMS TO MONITOR AND IDENTIFY EARLY NONADHERENCE ACTIVITY BASED ON VISUAL CONFIRMATION OF MEDICATION INGESTION**

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*<sup>1</sup>AiCure, <sup>2</sup>Takeda Development Center Americas, Inc.*

**Abstract:** Objective: Acute schizophrenia is characterized by the presence of active positive symptoms, which may be disruptive to the patient and increase the risk of medication nonadherence. This sub-study used an artificial intelligence (AI) platform to measure dosing compliance in subjects with schizophrenia in a Phase 2, randomized, double-blind, placebo-controlled study.

Methods: Subjects in the TAK-063 study who were stable after  $\geq 3$  weeks of inpatient treatment and discharged were followed up as outpatients for the remainder of the 6-week period. Subjects were given mobile devices with the AI application downloaded and asked to use the application during self-administration of study medication. Software algorithms based on computer vision automatically confirmed patient identity, the medication, and correct self-administration of the medication. Real-time dosing data (classified as taken, missed, self-reported on the device or by phone) were transferred to user-restricted web portal for real-time analysis and review. Nonadherence and incorrect usage of the application triggered alerts. The primary adherence measures for the study were based on scheduled pill counts and pharmacokinetic (PK) sampling (Weeks 1, 2, 3, and 6); AI platform data were tested for exploratory purposes.

Results: The AI platform was used by 26 subjects for 372 subject days, and 744 adherence parameters were collected. In subjects completing the trial (n=21), mean cumulative adherence rate based on visual confirmation of drug ingestion (AI application) was 82.5%. In comparison, pill count was 100.4%. For subjects receiving TAK-063 (n=12), mean cumulative adherence based on the AI application was 88.4%, while adherence based on pill count was 99.6%. Based on PK sampling at Week 6, average adherence was 91.7% (11 of 12 subjects had study drug concentrations above the lower limit of quantification [LLOQ]). Suspicious activity alerts were triggered during the trial in the subject with a Week 6 PK sample below LLOQ.

Conclusions: Mobile AI application was implemented in a Phase 2 clinical trial in adult subjects with acute exacerbation of schizophrenia. Subjects who were discharged from the inpatient setting and who completed the study demonstrated high rates of adherence using a mobile AI application. Data from this study support further use of mobile AI applications to monitor medication adherence in schizophrenia studies.

#### **T70. DASOTRALINE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: RESULTS OF A PHASE 2/3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY**

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**Abstract:** Background: Dasotraline is a novel and potent dopamine and norepinephrine reuptake inhibitor (DNRI) with slow absorption and a long half-life, resulting in stable plasma concentrations over 24 hours with once-daily dosing. Safety and efficacy of dasotraline have been demonstrated in a phase 2/3 study in adults with ADHD (NCT01692782). This study evaluated efficacy, safety, and tolerability of dasotraline in children aged 6–12 with ADHD (NCT02428088).

Methods: Children aged 6–12 years old meeting DSM-5 criteria for ADHD were randomized 1:1:1 to 6 wks of double-blind, once-daily, dasotraline (2 or 4 mg/d) or placebo. The primary efficacy endpoint was the change from baseline (CFB) in the ADHD Rating Scale Version IV Home Version (ADHD RS-IV HV) total score at Wk 6, analyzed using a mixed model for repeated measures (MMRM) in the intent-to-treat population. Secondary endpoints included ADHD-RS-IV HV at Wks 1-5 (and subscales at Wks 1-6), Clinical Global Impression-Severity scale (CGI-S), safety and tolerability, vital signs, and weight.

Results: Of the 342 patients randomized, mean age was 9.1 [ $\pm$ 1.9] years and 66.7% were male. Overall, 79% of patients completed the study; 87% of completers continued into a 26-wk open-label safety study (NCT02457819). Adverse events (AEs) were the most common reason for discontinuation (2 mg/d: 6.3%; 4 mg/d: 13%; placebo: 1.7%). In the intent-to-treat population (N=336), ADHD-RS-IV HV total score improved significantly from baseline to Wk 6 with dasotraline 4 mg/d vs placebo (least squares [LS] mean CFB:  $-17.53$  [95% CI:  $-20.12$ ,  $-14.95$ ] vs  $-11.36$  [ $-13.89$ ,  $-8.83$ ], respectively; effect size (ES): 0.48,  $p < 0.001$ ). With dasotraline 4 mg/d, a statistically significant difference from placebo treatment was maintained each wk through Wk 6. Additionally, both the inattentive and hyperactivity/impulsivity subscale scores were significantly improved with 4 mg/d vs placebo at Wk 6 ( $p = 0.001$  and  $p = 0.003$ , respectively). The 2 mg/d arm did not demonstrate a statistically significant difference from

placebo (LS mean CFB: -11.80 [-14.37, -9.22]; ES: 0.03, p=0.812). Improvements in CGI-S scores were statistically significant with 4 mg/d vs placebo at all time-points (Wk 6 LS mean CFB: -1.39 [-1.63, -1.15] vs -1.04 [-1.28, -0.80], respectively; ES: 0.29, p=0.040). The 2 mg/d dose did not separate at Wk 6 (LS mean CFB: -0.94 [-1.18, -0.70]; ES: 0.08, p=0.575). Treatment-emergent AEs (TEAEs) were generally mild or moderate in severity; the most frequent ( $\geq 5\%$  and greater than placebo) were (2 mg/d; 4 mg/d; placebo): combined insomnia (15.3%; 21.7%; 4.3%), decreased appetite (12.6%; 21.7%; 5.2%), weight loss (5.4%; 8.7%; 0%), irritability (3.6%; 7.0%; 6.0%), nasopharyngitis (0.9%; 5.2%; 0.9%), and nausea (0; 5.2%; 2.6%). Overall, 0.9%, 2.6%, and 1.7% of patients experienced severe TEAEs. There were no serious TEAEs. The TEAE most frequently associated with discontinuation was insomnia (1.8%; 3.5%; 0). Mean supine heart rate CFB at Wk 6 was (2 mg/d; 4 mg/d; placebo) 2.7, 6.1, and 1.6 bpm. Mean weight CFB at Wk 6 was (2 mg/d; 4 mg/d; placebo): -0.41, -1.19, and +0.95 kg.

Conclusions: Dasotraline 4 mg/d, but not 2 mg/d, significantly improved ADHD symptoms in children compared to placebo, as measured by ADHD-RS-IV HV total score and inattentiveness and hyperactivity/impulsivity subscale scores. Dasotraline was generally well-tolerated with an AE profile consistent with its DNRI mechanism of action. Studies evaluating longer term use are in progress.

## **T71. EFFICACY AND SAFETY OF LURASIDONE IN CHILDREN AND ADOLESCENT PATIENTS WITH BIPOLAR I DEPRESSION**

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**Abstract:** Objective: Bipolar I disorder has an estimated prevalence of 2.7% in adolescents, and <1% in children. Depression associated with bipolar disorder in children and adolescents is associated with high rates of suicide attempts, and high rates of recurrence and functional impairment. However, there are few evidence-based treatments available for youth with bipolar depression. (1,2) Lurasidone has been approved by the FDA for the treatment of bipolar depression in adults. The aim of this multi-regional study was to evaluate the efficacy and safety of lurasidone in children and adolescents with bipolar depression.

Methods: Patients ages 10-17 years of age with a DSM-IV-TR diagnosis of bipolar I depression were randomized to 6 weeks of double-blind treatment with once-daily, flexible doses of lurasidone in the range of 20-80 mg. Primary and key secondary endpoints were change from baseline to week 6 in the Children's Depression Rating Scale, Revised (CDRS-R) total score, and the Clinical Global Impressions, Bipolar Severity of Depression Score (CGI-BP-S), respectively, evaluated by mixed model repeated measures analysis.

Results: A total of 347 patients were randomized and received at least one dose of lurasidone (N=175; male, 50.3%; mean age, 14.2 years) or placebo (N=172; male, 51.7%; mean age, 14.3 years). Mean dose of lurasidone was 32.6 mg/d, with modal dose distribution of 51.8%, 26.5%, 12.9%, and 8.8% for 20 mg, 40 mg, 60 mg, and 80 mg, respectively. Treatment with lurasidone was associated with significantly greater week 6 improvement vs. placebo on the CDRS-R total score (-21.0 vs. -15.3; P<0.0001; effect size, 0.45), and the CGI-BP-S score (-1.49 vs. -1.05; P<0.0001; effect size, 0.44). Lurasidone was also associated with statistically significant and clinically meaningful improvement in secondary measures of anxiety, quality



of life, and global functioning. Study completion rates were 92.0% in the lurasidone group, and 89.7% in the placebo group; discontinuation rates due to adverse events were the same (1.7%) for both groups. The 3 most frequent adverse events reported for lurasidone vs. placebo were nausea (16% vs. 6%), somnolence (11% vs. 6%), and increased weight (7% vs. 2%). At study endpoint, a numerical reduction was observed in median fasting lipids values; no change was observed in fasting glucose or HbA1c; and an increase was observed compared with placebo in mean weight (+0.74 kg vs. +0.44 kg) and median prolactin (+ 1.10 vs. +0.50 ng/mL).

**Conclusions:** In children and adolescents with a diagnosis of bipolar depression, lurasidone (20-80mg/d) demonstrated statistically significant and clinically meaningful improvement vs. placebo on measures of depression severity (CSRS-R, CGI-BP-S) and on secondary measures of anxiety, quality of life, and global functioning. In this study, lurasidone was associated with few effects on weight and metabolic parameters, and was generally well-tolerated.

Clinicaltrials.gov identifier: NCT02046369

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## **T72. SHORT AND LONG-TERM EFFECTS OF LPS ON BEHAVIOR AND OXIDATIVE STRESS IN MALE AND FEMALE C57BL/6 MICE**

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**Abstract:** Introduction: The objective of the current study was to examine the effect of the endotoxin lipopolysaccharide (LPS) on oxidative stress and labile zinc in the hippocampus, within the context of a depressive-like episode, acutely and longitudinally. We hypothesized that LPS would induce oxidative stress, contributing to neuronal damage and, ultimately, hippocampal atrophy. Also, we expected females to be protected from the effect of LPS due to the anti-inflammatory properties of estrogen (E2).

Methods: Part 1- behavioral tests were performed on group housed (4 per cage) male (N=24) and female (N=24) C57BL/6 mice. 24 hours before behavioral testing, males and females were injected (IP) with either LPS (0.83 mg/kg, N=12) or saline vehicle (0.9% NaCl, N=12). The open field test (OFT) and the forced swim test (FST) were performed 24-28 hours after injection in the dark under red light. Brain tissue was either flash frozen in isopentane over dry ice or preserved in RNAlater (28-32 hours after injection). Right and left hippocampi were preserved for protein and mRNA analysis, respectively. All samples were stored at -80 °C until use. Part 2- a pilot study to examine longitudinal effects of LPS was performed on singly housed males given LPS (N=6) or saline (N=6). The FST was performed at three time points: 24 hours, 14 days and 28 days after injection. Tissue was harvested after the last behavioral test.

Results: Part 1- Depressive-like behavior was evident in males 24 hours after LPS ( $p<.01$ ). Histological staining for a marker of oxidative DNA damage, 8-OHdG, revealed a significant interaction between sex and LPS,  $F(1, 10) = 4.984$ ,  $p=.049$ . Tukey's post hoc analysis revealed a significant increase ( $p<.01$ ) in 8-OHdG staining in the CA3 region in males compared to females given LPS. Quantitative PCR revealed males increased ( $p<.01$ ) mRNA for a protein that buffers intracellular oxidative stress, metallothionein II, after LPS. Part 2- Repeated measures ANOVA revealed a significant effect of LPS ( $p=.03$ ) and time ( $p<.0001$ ) on male behavior in the FST. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)

staining revealed significantly increased levels of apoptotic cells in the hippocampus after LPS ( $p < .01$ , CA3). There was also increased levels of cleaved caspase-3 protein in the hippocampus after LPS ( $p = .02$ ). Moreover, we found decreased mBDNF protein ( $p = .03$ ) in the hippocampus 28 days after a single LPS injection.

**Summary:** The current study revealed that male mice appear to experience depressive-like behavior, as well as oxidative stress in the hippocampus, after systemic administration of LPS. Also, female mice were resistant to acute deleterious effects of LPS. Interestingly, labile zinc homeostasis may have been altered in both males and females in response to LPS, though the role of zinc was not fully elucidated in this model. Further, neurogenesis was reduced, and markers of apoptosis increased, in the hippocampus of males long-term. Future work will aim to understand more fully the role of labile zinc and oxidative stress in depressive states acutely and chronically, and the sex differences that may exist therein. In this way, we may chart a better course for understanding this widespread, multifaceted mood disorder.

### **T73. IS PARITY A PROTECTIVE FACTOR AGAINST SUICIDE ATTEMPTS IN WOMEN WHO HAVE EXPERIENCED SEXUAL VIOLENCE?**

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**Abstract:** Background: Sexual violence is a relevant issue in public health. In Ecuador, statistical data INEC, show that 6 out of 10 women have experienced some form of gender violence, 1 out of 4 have suffered sexual violence. There is a clear association between reported sexual violence and reported suicide attempt. Women who experienced sexual assault in childhood or adulthood are more likely to attempt or commit suicide than other women. Prior studies have identified factors that may or may not contribute to these suicide attempts such as age, education, post-traumatic stress disorder and other psychiatric disorders. Previous researches have indicated that parity may be a protective factor against suicide attempts or suicide. Objectives: The aim of this study is to explore whether parity is a protective factor against suicide attempts in women who have suffered from sexual violence or not. Methods: We conducted a retrospective, transversal descriptive study with information extracted from the National Institute of Statistics and Census (INEC) web page. This data base consisted in 36328 women from 15 years old and ahead. They performed this survey from November 16 to December 15 of 2011. The sample was 737 women who suffered sexual violence. These women were classified by their marital status: single, married and separated women. We compared the women who had children and the ones who didn't with the women who committed suicide attempts and the ones who didn't. Results: 737 women in this study. 281 married, 248 separated and 208 single. Results: suicide attempts, married women with children 177 (62.99%), no children 7 (2.49%), Chi-Square Test:  $P = 0.7595$  ( $p > 0.05$ ); suicide attempts. Separated women with children 110 (44.35%), no children 86 (34.68%), Chi-Square Test:  $P = 0.0000$  ( $p < 0.05$ ); suicide attempts single women with children 59 (28.37 %), no children 106 (50.96%), Chi-Square Test:  $P = 0.3335$  ( $p > 0.05$ ). Odds Ratio for married women 1.23917, separated women 0.209756, single women 0.695462. Conclusions: This study provides evidence that support parity as a non-protective factor against suicide attempts in women who have suffered sexual violence. These results are a clear cut demand to mental health organizations to develop programs to prevent and protect women that have faced this type of violence, not only for the victims but also for the children who confront a risky situation.

#### **T74. ADULT GLUCOCORTICOID RECEPTOR MRNA IN RESPONSE TO AN ACUTE STRESSOR: ROLE OF CSF CORTICOTROPIN-RELEASING FACTOR IN HPA AXIS REGULATION FOLLOWING EARLY LIFE STRESS**

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**Abstract:** Introduction: Early life stress (ELS) has been shown to play a role in establishing persistent maladaptive HPA axis modifications that may contribute to the pathogenesis of mood and anxiety disorders. Central glucocorticoid receptor (GR) messenger RNA (mRNA) expression may facilitate neuroadaptation to ELS. The role of monocytic GR mRNA expression, a putative CNS proxy, during acute stress exposure and post-stress was explored as well as the ELS marker, cerebrospinal fluid (CSF) corticotropin-releasing factor.

Methods: Six adult macaques (three of which were exposed to variable foraging demand, a form of ELS) underwent acute restraint. Baseline GR expression and plasma cortisol concentrations were measured followed by subsequent measurements following stress completion (t=0 minutes, 4 hours, 5 days & 7 days). CSF CRF concentrations were obtained in 5 subjects as juveniles to determine its association with GR expression in response to stress.

Results: As expected acute restraint stress produced a significant increase in plasma cortisol concentrations most robust at four hours post-stress time point. There was a significant juvenile CSF CRF concentrations x time interactive effect in predicting adult serial GR expression (partial  $\eta^2 = 0.80$ ). During acute stress juvenile CRF concentrations negatively predicted GR expression and during recovery, “flipped” to positively predict expression. Juvenile CSF CRF concentrations positively correlated with the magnitude of overall change in GR expression.

Conclusions: During acute stress, relatively high CSF CRF concentrations are associated with relatively rapid reductions in GR expression. Return to an ambient post-stress state was characterized by a direct relationship between juvenile CSF CRF concentration and adult monocytic GR expression, consistent with increased HPA axis restraint in high CRF subjects. An ELS-associated allostatic adaptation suggests relative elevations of juvenile CSF CRF concentration set the stage for a relative hyperplasticity of GR expression in response to acute stress with potential long-term effects on HPA axis regulation.

#### **T75. NETWORK ANALYSIS OF DEPRESSIVE AND MANIC SYMPTOMS IN STEP-BD STUDY**

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**Abstract:** Background: Bipolar disorders are characterized by mood swings that involve episodes of mania and depression, and changes in sleep, energy, thinking and behavior. This study applies network analysis approach to examine the interactive effects of depressive and manic features at the level of individual symptoms, using data from the National Institute of Mental Health’s Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study.

We tested the hypotheses that “sleep disturbance” symptom, an overlapping symptom in depressive and manic features, explained, in part, the complex presentations of manic-depressive illness.

Methods: Patients in STEP-BD who met DSM-IV criteria for bipolar I or bipolar II were included in this analysis (N=3750). We applied the partial correlation network model with graphical LASSO to analyze the interactive relationships of MADRS and YMRS items. Pair-wise partial correlations between symptoms were tested using Holm multiple testing procedure at alpha 0.001.

Results: The overall network shows clustering patterns of depressive and manic symptoms (nodes) within the disorder, and significant direct connections across the disorders through the overlapping “sleep” symptoms (bridge symptom). MADRS “reduced sleep” symptom had significant direct relationships (as assessed by partial correlations) with the following YMRS symptoms: “increased motor energy”, “language and thought disorder”, “irritability”, and “disruptive aggressive behavior”. YMRS “reduced sleep” symptom had significant direct relationships (as assessed by partial correlations) with the following MADRS symptoms: “reduced appetite”, “lassitude”, “inability to feel”, “concentration difficulties”, “inner tension”, and “apparent sadness”. Three additional significant cross disorder paths were found between MADRS and YMRS items. Presence of "sleep-sleep" link (MADRS "sleep" item score >0 or YMRS "sleep" item score > 0) was found in 47% of patients. Increased depression-mania links (1 - 4) was associated with greater symptom severity, as assessed by MADRS and YMRS scores.

Conclusion: Our findings suggest that network model is a useful approach for identifying symptom networks and pathways that connect depressive and manic mixed features in bipolar disorders.