

# POSTER ABSTRACTS

## NEW APPROACHES TO MENTAL ILLNESS IN THE ERA OF THE NATIONAL BRAIN INITIATIVE



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# Tuesday, June 17, 2014

## Poster Session 1

P-1

### **A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP, DOSE FREQUENCY STUDY OF INTRAVENOUS KETAMINE IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION**

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Background Ketamine has been shown to produce rapid antidepressant action in patients with treatment-resistant depression (TRD). The purpose of this phase 2 trial is to evaluate if twice weekly (2X/wk) dosing will be as efficacious as 3 times per week (3X/wk) in sustaining the antidepressant effects of ketamine. Methods Patients with TRD were randomized 1:1:1:1 to receive one of 4 intravenous 4-week treatments: 2X/wk or 3X/wk placebo, or 2X/wk or 3X/wk ketamine (0.5mg/kg as an infusion over 40 minutes). The primary efficacy endpoint was the change from baseline to Day 15 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Safety and secondary efficacy endpoints were also assessed. Results Sixty-seven (intent-to-treat) patients were enrolled. The mean age was 44 years and the average baseline MADRS total score was 35. The primary efficacy endpoint showed significant improvement in the MADRS total score for both ketamine dose frequency groups compared with corresponding placebo groups ( $p < 0.001$  in both groups, 1-sided). The differences of least squares mean (SE) change from baseline between ketamine and placebo were -16.0 (3.74) for the 2X/wk group and -16.4 (2.40) for the 3X/wk group. During the double-blind treatment phase, the most common ( $\geq 20\%$  of patients) treatment-emergent adverse events were headache, anxiety, dissociation, nausea, and dizziness. There were 2 non drug-related serious adverse events (anxiety and suicide attempt) in the ketamine 2X/wk group. No death was reported. We will also review data for a second study (efficacy and safety). Conclusions Ketamine dosed 2X/wk or 3X/wk demonstrated similar efficacy and significant changes in the MADRS total score from baseline to Day 15, and was generally well tolerated.

#### **Learning Objectives:**

- Attendees will learn about challenges of developing a new drug with a novel MOA.
- Attendees will learn about combination of drug-device development.

P-2

### **A PILOT STUDY OF A NOVEL MONOAMINE TRIPLE REUPTAKE INHIBITOR EB-1020 SR IN THE TREATMENT OF ADHD IN ADULTS**

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Background: This pilot study was designed to evaluate EB 1020-SR as a novel non-stimulant treatment option for adult attention-deficit hyperactivity disorder (ADHD). EB1020-SR is a norepinephrine-preferring triple reuptake inhibitor with IC50 values for transporter reuptake

inhibition of 6 nM, 38 nM, and 83 nM, for norepinephrine, dopamine and serotonin respectively. Methods: A total of 41 adult males with well-characterized ADHD enrolled in this 4-week, single-blind study with 1-week placebo run-in. EB1020-SR was given twice daily and titrated to a target dose of 500 mg daily over 7 days. Outcomes assessed included ADHD, executive functioning, and tolerability. Results: 37 subjects completed the trial. EB 1020-SR produced a 21-point reduction on the ADHD Rating Scale-IV (endpoint mean score =17,  $p<0.0001$ ) including significant reductions in inattentive ( $p<0.0001$ ) and hyperactive impulsive symptoms ( $p < 0.0001$ ). Overall, 68% of subjects were considered responders using the Clinical Global Impression of Improvement (much/very much improved). Clinically and statistically significant improvements in overall and specific domains of executive function using the Behavioral Inventory of Executive Functioning were also found (overall  $p<0.0001$ ). No clinically meaningful trends in adverse events, laboratory values, vital signs, or ECG parameters were noted. Conclusions: EB 1020-SR appears effective in treating ADHD and executive functioning deficits in adult males. The maximum dose studied appears to be well tolerated. Based on these results, randomized, controlled studies of EB 1020 appear warranted.

P-3

### **AZD8529, A POSITIVE ALLOSTERIC MODULATOR OF THE MGLUR2 RECEPTOR FOR THE TREATMENT OF SCHIZOPHRENIA**

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Compelling evidence indicates that hypo function of prefrontal cortex glutamate signaling may play an important role in schizophrenia. This is likely due to decreased activation of NMDA receptors located on GABAergic interneurons, resulting in a lack of downstream inhibition and disruption of cortical circuit activity. Activation of the mGluR2 receptor is proposed as a novel therapeutic strategy for schizophrenia, based on the hypothesis that this mechanism would counteract the glutamatergic disinhibition produced by NMDA receptor hypo function. Activation of mGluR2 has been shown to reduce the working memory deficit induced by ketamine and one study showed an antipsychotic effect in acute schizophrenia, an effect not reproduced in subsequent studies. AZD8529 acts as a selective positive allosteric modulator of mGluR2, it potentiated the effects of glutamate at the recombinant human receptor with an EC<sub>50</sub> of 193 nM and an E<sub>max</sub> of 93% with little effect on other mGluR subtypes. In a rat hippocampal slice assay, AZD8529 enhanced DCG-IV-induced reduction in synaptic transmission at hippocampal Schaffer collateral synapses by 30%, with an EC<sub>50</sub> of 87 nM. Administration of AZD8529 (10  $\mu$ mol/kg, s.c.) caused a modest (<10%), reduction in baseline firing of mPFC neurons in behaving rats. MK-801 (0.2 mg/kg, s.c.) led to an increase in firing rates of recorded neurons, accompanied by a profound disturbance in organization of cortical firing as measured by a large increase in the variability of firing rates. Administration of AZD8529 significantly reversed the MK-801-induced increase in firing rate variance reflecting a normalization of cortical function. AZD8529 was well tolerated in human volunteers, with CNS drug exposure confirmed through csf analysis. In human translational imaging studies, effects consistent with CNS mGluR2 activation were observed at clinically relevant plasma drug exposures. AZD8529 was examined in a proof of principle study in symptomatic patients with schizophrenia Following 7 days washout period, patients received AZD8529 40mg (n=58), risperidone 4mg (n=31), or placebo (n=55) for 28 days, clinical efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS). Whilst risperidone reduced PANSS total score change from baseline compared with placebo ( $D=-9.5$ ,  $p<0.001$ ), AZD8529 was without effect ( $D=1.3$ ,

p=0.491). The current data are not consistent with positive modulation of mGluR2 receptors as a mechanism for monotherapy to treat acute schizophrenia. It remains to be determined whether different treatment regimens and particularly adjunct treatment would provide benefit.

P-4

**EFFICACY AND SAFETY OF A NOVEL MGLU2 RECEPTOR POSITIVE ALLOSTERIC MODULATOR AS AN ADJUNCTIVE TREATMENT TO AN SSRI/SNRI IN THE TREATMENT OF ANXIOUS DEPRESSION**

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This presentation will discuss the recent results of a Phase 2a proof-of-concept study of a novel mGluR2 positive allosteric modulator (PAM) in the adjunctive treatment of Major Depressive Disorder (MDD) with significant anxious features. This was a multicenter, double-blind, placebo-controlled, flexibly-dosed study of an mGluR2 PAM in adult patients with MDD with significant anxious symptoms. The study consisted of 3 phases: a screening phase of up to 2 weeks, an 8-week double-blind treatment phase (including two 4-week treatment periods), and a 2-week posttreatment follow-up phase. Methods: Entry requirements for patients included: DSM-IV diagnosis of MDD, Hamilton Depression Rating Scale-17 (HDRS-17) score of  $\geq 18$ , HDRS Anxiety Somatization Factor score of  $\geq 7$  (to ensure adequate level of anxiety), and current treatment with an SSRI/SNRI at an adequate dose for a minimum of 4 weeks at screening, and a maximum of 12 weeks, with insufficient response. Comorbid Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and Panic Disorder (PD) were allowed. A doubly-randomized design was employed. At entry into Period 1, patients were randomly assigned in a 1:1 ratio to the mGluR2 PAM or Placebo as adjunctive treatment to their baseline antidepressant therapy. The mGluR2 PAM drug was flexibly dosed in the range of 50mg to 150mg b.i.d. At the end of Period 1, those patients exposed to Placebo who continued to meet severity criteria (HDRS-17 score  $\geq 18$  and HDRS Anxiety Somatization Factor score of  $\geq 7$ ) were re-randomized in a 1:1 ratio to mGluR2 PAM or Placebo. All other subjects underwent a sham re-randomization and continued on their same treatment. Results: Of 121 subjects randomized, 107 entered Period 2, during which 22 subjects treated with Placebo in Period 1, and meeting the criteria for nonresponse, were re-randomized. No efficacy signal was detected on the primary outcome measure, the 6-item Hamilton Anxiety Scale (HAM-A-6), based on the weighted combination test (p=0.51); however, efficacy signals were evident on several secondary outcome measures of both depression (HDRS-17 total score, 6-item subscale of HDRS-17 assessing core depressive symptoms (HAM-D-6), Inventory of Depressive Symptomatology (IDS-C30) and anxiety (HDRS Anxiety Somatization Factor, IDS-C30 Anxiety Subscale). The drug demonstrated a benign safety profile and was well-tolerated, with the most common treatment emergent adverse events being dizziness-related events. Conclusions: The totality of data do not suggest a strong drug effect for this mGluR2 PAM in the adjunctive treatment of anxious depression. Although glutamatergic mechanisms are felt to play a role in this disorder, administration of an mGluR2 PAM in the dose range tested did not appear to have a clinically significant impact on symptoms. Overall, the drug was safe and well-tolerated in the dosing range studied. Learning Objectives: 1. Participants will understand the rationale for treatment approaches aimed at modulating glutamatergic neurotransmission in the anxious depressed population. 2. At the conclusion of this session, participants will be aware of the

results of a proof-of-concept study with a novel mGluR2 PAM, and understand the impact of these results on further pursuit of this target in depression.

P-5

## **LUPRON IN COMBINATION WITH AN ACETYLCHOLINESTERASE INHIBITOR HALTS COGNITIVE DECLINE IN WOMEN WITH ALZHEIMER'S DISEASE OVER A 48 WEEK PERIOD**

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Context: Evidence for suppressing gonadotropin-releasing hormone (GnRH) and gonadotropin signaling in the treatment of Alzheimer's disease (AD) comes from a growing number of epidemiological, preclinical and biological studies. Objective: To determine the efficacy and safety of suppressing GnRH and gonadotropin signaling with leuprolide acetate (Lupron Depot®) in the treatment of women with mild to moderate AD. Design: A 48 week, double-blind, placebo-controlled, dose-ranging study conducted in women aged 65 years or older with mild to moderate AD. Setting: Five study sites in the United States. Participants: A total of 109 women with mild to moderate AD and a Mini-Mental State Exam score between 12 and 24 inclusive. Interventions: Participants were randomized to low dose Lupron Depot® (11.25 mg leuprolide acetate), high dose Lupron Depot® (22.5 mg leuprolide acetate) or placebo injections per 12 weeks. Main Outcome Measures: The primary efficacy parameters were the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC). Secondary efficacy parameters were the Neuropsychiatric Inventory (NPI), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL), Burden Interview (BI), and ADCS-Severity Rating. Results: In the primary analysis there was a trend, although not statistically significant, in favor of the high dose Lupron group on the ADAS-Cog. The mean decline in the ADAS-Cog scores after 48 weeks of treatment in the placebo, low- and high-dose groups were 2.4, 4.9 and 1.7, respectively. A similar, although not as pronounced trend, was observed for ADCS-CGIC scores. The number of patients who exhibited a decline in CGIC scores in the placebo, low- and high-dose groups were 20 (54%), 26 (72%) and 18 (39%), respectively. There were no statistically significant differences in any of the secondary efficacy parameters. However, in the apriori designated subgroup analysis of patients taking an acetylcholine esterase inhibitor (AChEI) there was a statistically significant benefit as determined by ADAS-Cog, ADCS-CGIC and ADCS-ADL in the high dose group compared to both the low dose and placebo groups. The mean decline in ADAS-Cog after 48 weeks in the high-dose group was 0.18 compared to those taking low dose 4.21 and placebo 3.30. Similarly, on the ADCS-CGIC 38% percent of subjects experienced decline in the high-dose group compared to 82% in the low dose group and 63% in the placebo group. The mean decline in the ADCS-ADL in the high dose group was -0.54 compared to -8.00 and -6.85 in the low dose and placebo groups respectively. No differences between treatment groups were seen on the NPI, ADCS-CGI Severity Rating, or the BI in the subgroup analysis. Conclusions: Cognitive function was preserved in patients treated with high dose Lupron who were already using AChEI's. However, caution should be used in the interpretation of the results due to the fact that; the study size is small, baseline demographics were not compared for the subgroup, and the data was not adjusted for multiple analyses. The positive interaction between Lupron and AChEI's warrants further investigation for the treatment of AD.

P-6

**RESULTS OF A PHASE 2B CLINICAL TRIAL OF TC-5619, A SELECTIVE ALPHA 7 NEURONAL NICOTINIC RECEPTOR (NNR) AGONIST IN THE ADJUNCTIVE TREATMENT OF NEGATIVE SYMPTOMS AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA**

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Background: There are no approved medicines to treat negative symptoms or cognitive dysfunction in people with schizophrenia. These are common features of the condition that often prevent those whose positive symptoms are well-controlled from resuming or achieving their premorbid potential. TC-5619, a selective alpha 7 NNR agonist, showed statistically significant benefit in preclinical models of cognition and negative symptoms; and also showed statistically significant benefit in cognitive and negative symptoms in an early phase 2 adjunctive clinical trial in schizophrenia that was conducted in the US and India. Methods This phase 2B clinical trial was a double-blind, randomized, parallel group, fixed dose, placebo-controlled trial comparing TC-5619 vs. placebo in the adjunctive treatment of negative symptoms or cognitive dysfunction in well-controlled outpatients with schizophrenia. Sixty-six sites in the US, Russia, Ukraine, Hungary, Romania and Serbia randomized 477 patients into a 24-week treatment period in which they received either TC-5619 (5 mg or 50 mg po qd) or placebo in a 1:1:2 ratio. All atypical antipsychotics were permitted except clozapine. The primary endpoint, negative symptoms, was measured using the Scale to Assess Negative Symptoms (SANS), and the key secondary endpoints, cognition and functional ability, were measured using the Cogstate Schizophrenia Test Battery (CSTB) and the UCSD Performance-Based Skills Assessment-Brief version (UPSA-B). A variety of other endpoints included global clinical outcome, adverse events, vital signs, physical exam, laboratory and ECG measurements, movement disorders, suicidality, depression, and tobacco craving. Results: The majority of the randomized subjects were tobacco users and the demographic profile was consistent with other trials in this population. None of the primary, key secondary or secondary efficacy outcome measures showed a statistically significant benefit favoring either dose of TC-5619. Withdrawals of any kind including those due to adverse events were low, and there were few serious adverse events. The previously established safety and tolerability profile was not altered by any unanticipated findings. Discussion: This well-conducted and robust phase 2B study did not confirm benefits of TC-5619 in negative or cognitive symptoms, but it did confirm that the compound was generally safe and well-tolerated. Reasons for the lack of benefit do not appear to include dose selection, site performance, or subpopulation factors.

P-7

**A RAPIDLY ACTING INTRANASAL TREATMENT FOR THE SYMPTOMS OF GAD**

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Although generalized anxiety disorder (GAD) is a common and sometimes disabling condition, there is a need for additional treatments other than benzodiazepines that can be used on a prn basis to help with the severe anxiety and distress that many affected individual's experience. PH94B is a new investigational drug for the acute treatment of Social Anxiety Disorder. Chemically, PH94B is an odorless, neuroactive steroid compound with proven lack of affinity to

steroidal hormone receptors. It is thought to act via nasal chemosensory receptors that broadcast chemosensory information to specific brain areas (cingulate gyrus, hypothalamus, limbic amygdala, anterior gyrus and prefrontal cortex) which are different from the brain areas activated by olfactory stimuli. Earlier studies demonstrated that picomol quantities of PH94B induced dose-dependent membrane currents and increased  $\text{Ca}^{2+}$  in isolated human nasal chemosensory cells, and depolarization of the human nasal chemosensory epithelium, followed by small but significant decreases in heart rate, respiratory rate, electrodermal activity, and blinking reflex, and increased alpha-EEG and body temperature. A number of the volunteers spontaneously reported feeling distinctly calm and less nervous during these studies. Similar results were obtained in a Phase I dose escalation study. To continue this exploration of PH94B, 28 patients with GAD (DSM-IV) were enrolled in a randomized, placebo-controlled, double blind study. Following exclusion of placebo responders ( $n = 7$ ) 21 patients were randomized to receive 200 pg PH94B or placebo in a one second aerosol pulse to the chemosensory epithelium of the anterior nasal septum. HAM-A, and clinical electrophysiological measures were administered at randomization (Baseline) and 30 and 60 min following treatment. Because of the small sample size and lack of power, effect sizes (Cohen's  $d$ ) were evaluated in addition to between-group comparisons. Nineteen completed the study (2 early terminators). Thirty minutes after treatment there was mean reduction of 32.0% (8.7 points) for the PH94B group ( $n = 11$ ) and 19.6% (5.1 points) for the Placebo group ( $n = 8$ ) in total HAM-A ( $p = 0.09$ , one-tail  $t$ -test; Cohen's  $d = 0.644$ ). Electrophysiological changes (respiratory, cardiac, and electrodermal frequency), concordant with the reduction in anxiety, were significantly greater for the PH94B group ( $p$ 's  $< 0.003$ , one-tail; Cohen's  $d$  range: 1.3 to 8.0). Further exploration of group differences for individual HAM-A item scores revealed impressive effect sizes for improvement in Anxious Mood Cognition Depressed Mood Cardiovascular Symptoms and Other Autonomic Symptoms (Cohen's  $d$  range: from 0.469 to 1.59). After 60 min, all significant improvements and group differences had disappeared. PH94B may be useful as a prn treatment for GAD, although further trials with larger samples are indicated. PH94B may be useful in other anxiety states where rapid, temporary relief would be of benefit, like performance and social anxiety that is part of social anxiety disorder. In fact, this was recently demonstrated in a placebo controlled trial. Nasal chemosensory cells may be a portal of entry for substances affecting feeling states.

P-8

### **METADOXINE EXTENDED RELEASE (MDX): A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF ADHD & OTHER COGNITIVE DISORDERS**

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Psychostimulants comprise the majority of the therapeutic landscape for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). However, some individuals may not respond or tolerate stimulants, some domains are less responsive to stimulants, and stimulants raise concerns for potential substance misuse or diversion. Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is an ion-pair salt of pyridoxine (vitamin B6) and 2-pyrrolidone-5-carboxylate (PCA, also known as L-PGA). Pyridoxine is a precursor of coenzymes such as pyridoxal phosphate. Pyridoxal phosphate-dependent enzymes are vital in the biosynthesis of the neurotransmitters serotonin, epinephrine, norepinephrine, and GABA. Metadoxine does not increase levels of brain neurotransmitters such as dopamine, norepinephrine and serotonin. In animal studies, Metadoxine has shown no signs of abuse or addiction potential. Metadoxine

Extended Release (MDX) is a novel, immediate release and sustained release formulation in a bi-layer tablet. An open-label study of MDX in 40 adults with ADHD demonstrated efficacy on the Conners Adult ADHD Rating Scale (CAARS) and the Test of Variables of Attention (TOVA) and was generally well tolerated. We now report on two double-blind placebo controlled Phase 2 studies of MDX in adults with ADHD. A 6-week, randomized, double-blind, parallel comparison of 1400 mg MDX vs placebo in 120 adults with ADHD showed significant improvements in weekly-assessed CAARS Total ADHD Symptoms Score ( $-12.5 \pm 1.18\text{SE}$  versus  $-8.93 \pm 1.24$ ,  $P < 0.02$ ) and TOVA ADHD score ( $5.07 \pm 1.19$  versus  $3.01 \pm 0.86$ ,  $P < 0.02$ ). Improvements were statistically significant compared with placebo after 2 weeks. A sub-analysis of subjects with ADHD inattentive type ( $n=48$ ) showed an even greater improvement in CAARS scores for subjects receiving MDX compared with placebo ( $-13.4 \pm 1.9$  versus  $-6.3 \pm 1.4$ ,  $P < 0.05$ ). Another randomized, double-blind, placebo-controlled, trial was conducted using a crossover design. This single-center study in 36 adult subjects with ADHD-PI evaluated MDX 700 mg, MDX 1400 mg, and placebo, each administered 1 week apart. TOVA assessments were performed 3 to 5 hours post-dose. The primary outcome was change from baseline in the TOVA ADHD score, which was statistically significant from baseline for MDX 1,400 mg compared with placebo (mean change 2.0, SD 4.2,  $P = .009$ ). There were no serious adverse events or any meaningful differences in adverse events profile between the drug and placebo groups. MDX may provide an important new treatment option for ADHD and other cognitive disorders with a rapid onset of effect and demonstrated efficacy in adult subjects with ADHD, particularly in patients with predominantly inattentive type ADHD, and an enhanced safety and tolerability profile. Learning Objectives: • Participants will learn about a new drug candidate, Metadoxine Extended Release (MDX), as a novel treatment for ADHD with attributes that may contribute to an enhanced efficacy, tolerability, and safety profile. • Participants will learn about the pharmacological profile of Metadoxine Extended Release (MDX), a non-dopaminergic, non-noradrenergic agent.

1

## **MEMANTINE IN THE TREATMENT OF EXECUTIVE FUNCTION DEFICITS IN ADULTS WITH ADHD: A PILOT RANDOMIZED DOUBLE BLIND CONTROLLED CLINICAL TRIAL**

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**Objective:** To evaluate the efficacy and safety of memantine hydrochloride as an adjunct to stimulant pharmacotherapy for treating executive function deficits (EFDs) in adults with ADHD. **Method:** This was a 12-week, double blind, placebo controlled, randomized clinical trial of memantine added to open label treatment with stimulant medication. Because of the small sample size, we considered a standardized mean difference (SMD; equivalent to effect size) of  $>0.5$  and odds ratios  $>2$  as indicators of trend improvements. **Results:** Twelve subjects received memantine and 14 received a placebo. Trend improvements favoring memantine were observed on: BRIEF-A Inhibition and Self-Monitor subscales and on the CANTAB: IED Total Errors, RTI Mean Simple Reaction Time, RTI 5 Choice Simple Reaction Time, RVP Probability of False Alarm, SOC Problems Solved in Minimum Moves, when compared to Placebo. **Conclusion:** Among adults with ADHD and EFDs, adjunct treatment with memantine to OROS-MPH was associated with improvements in selective areas of executive functioning, supporting the need for further research.



## Learning Objectives:

- The audience will learn that the anti-dementia medicine memantine has activity in treating executive function deficits in adults with ADHD.
- The audience will learn that the combination of memantine and stimulants is very well tolerated in adults with ADHD.

**Source of Funding:** This research was funded by a grant to Dr. Biederman from the Pond Family Foundation/APSARD ADHD Research Fund.

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## EFFECTS OF LISDEXAMFETAMINE DIMESYLATE ON BRAIN REWARD CIRCUITRY IN ADULTS WITH ADHD

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Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder which often persists across the lifespan. Historically, ADHD symptoms were attributed to inhibitory control deficits. However, recent evidence also implicates dopaminergic dysfunction within the motivation-reward system (e.g., Volkow et al., 2011). Thus, it is essential to understand the effects of stimulants on this network. The objectives of this fMRI study were: 1) to determine the effects of lisdexamfetamine dimesylate (LDX) on components of the brain motivation-reward system; and 2) to examine the relationship of these effects to clinical improvement. Data presented here are from an interim analysis on 15 subjects; the presentation at ASCP will report on the final sample (n = 20). Methods Fifteen adults with ADHD (age range: 19 – 50; 9 males) were treated with LDX and Placebo in a randomized, placebo-controlled, cross-over design. Each participant received active drug for 3 - 5 weeks via an escalating stepped dose titration. Subjects were scanned twice while performing a passive-avoidance learning task (White et al., 2013), after 3 – 5 weeks on active medication (LDX) or on Placebo. The task consists of a series of line drawings, and subjects learn to respond to/or avoid responding to images associated with a higher chance of winning/or losing money. The blood-oxygen-level-dependent (BOLD) signal was modeled using regressors for the images at the time of the decision (chosen vs. refused), and for the outcome (reward or punishment). Parametric modulators of these regressors accounted for the expectation that the participant had for the image, and for the prediction error corresponding to the feedback message. The extent threshold was 50 voxels, and  $p < .01$ . Regression analyses examined the association of regional activation during fMRI with clinician ratings of ADHD symptoms using the ADHD Rating Scale with adult prompts. Results Compared to Placebo, LDX increased modulation of BOLD responses in: 1) caudate and anterior cingulate cortices, when choosing to respond, and 2) insular/inferior frontal cortex, when refusing to respond. LDX also increased the modulation of BOLD responses by prediction error in the caudate when a reward was received. Increased caudate activation when choosing to respond with LDX was correlated with greater improvement in ADHD-RS scores. Conclusion Findings indicate that: 1) LDX increases sensitivity in the motivation-reward system, and 2) clinical improvement with LDX is associated with enhanced sensitivity to motivation-reward. These data expand our understanding of the mechanism of action of LDX and the manner through which it produces clinical improvement. References Volkow ND; Wang GJ;

Newcorn JH; Kollins SH; Wigal TL; Telang F; Fowler JS; Goldstein RZ; Klein N; Logan J; Wong C; Swanson JM: Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. *Mol Psychiatry* 2011; 16(11):1147-54 White SF; Pope K; Sinclair S; Fowler KA; Brislin SJ; Williams WC; Pine DS; Blair RJ: Disrupted expected value and prediction error signaling in youths with disruptive behavior disorders during a passive avoidance task. *Am J Psychiatry* 2013; 170(3):315-23

### **Learning Objectives:**

- To determine the effects of Lisdexamfetamine dimesylate (LDX), an FDA-approved stimulant medication in the US, on components of the brain motivation-reward system.
- To examine the relationship of these effects to clinical improvement over the course of treatment.

**Source of Funding:** Shire Pharmaceuticals, Inc.

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### **THE METHYLPHENIDATE-ATOMOXETINE CROSSOVER STUDY IN ADHD YOUTH: MEASURING AND COMPARING RESPONSE**

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Few studies have examined comparative efficacy of stimulant and non-stimulant children with ADHD in the same children using a crossover methodology. We directly compared these two medications in a head to head study using a range of doses to approximate "real-world" conditions, and examined the relationship between symptomatic improvement and patient preference at the end of the study. A randomized order, double-blind, crossover design was utilized where patients were treated for approximately 6 weeks and had a placebo washout before starting the second medication. Inclusion criteria were ADHD diagnosis (any subtype) based upon K-SADS, IQ. 75, and no medical contraindications. The study sample consisted of 232 children between 7-17 were randomized and 199 completed the study. Mean dose at end of treatment evaluations was 54 mg. OROS Methylphenidate (MPH) (range 18-72) and 1.35 mg/kg atomoxetine (ATX). With both treatment blocks combined, MPH was associated with an average decrease in ADHD RS score of 19.18, while atomoxetine was associated with an average decrease of 15.5. The effect size for the difference between treatments was -.23. At the end of the study, 102 children preferred MPH, 68 preferred ATX, and 29 chose neither. The largest number of youth responded to both medications. Preference was strongly related to being an excellent responder. At the group level, MPH was associated with a better symptomatic response and was preferred by more families. However, at the individual level, there was considerable variability in response and preference. ATX was associated with a better response when tried first then when tried second. Non-responders to moderate responders to ATX were likely to have a better response to MPH. Thus, a case could be made for trying either MPH or ATX first. Limitations include the complexity of a crossover design and order effects which are modeled in the analysis and the treatment duration of 6 weeks which may have favored MPH. Pending moderator analysis and examination of secondary outcome measures of response and tolerability may change implications for algorithm development.

### **Learning Objectives:**

- Increase familiarity with stimulant and non-stimulant treatment of ADHD and comparative efficacy.
- Highlight the advantages of a crossover study in being able to measure and predict response to treatment in the same patients, including differential response.

**Source of Funding:** NIMH-RO1, R01 MH70564-01A1 (M, Stein, PI), 3/1/05-12/10

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## **THE ROLE OF ALDOSTERONE AND CORTISOL IN ALCOHOL USE DISORDERS IN A BACLOFEN TREATMENT STUDY**

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Hormones of the adrenal cortex, specifically cortisol and aldosterone have been identified in numerous studies to play a significant role in the course of alcohol use disorders (AUD). Specifically, alcohol is viewed as a physiological stressor, which, similar to psychosocial stressors increases glucocorticoid levels. Patients with AUD have an attenuated cortisol response to stress when compared to social drinkers. Early alcohol withdrawal is marked by elevated cortisol levels while late withdrawal is marked by low levels of cortisol. In early abstinence, it is thought that low levels of cortisol is a predictor of relapse. Aldosterone levels are increased during alcohol withdrawal, and were found to correlate with craving scales. Baclofen has been investigated as a treatment modality for AUD and its effectiveness has been supported in many trials. The current study aims at investigating dysregulations of HPA hormones as biomarkers of alcohol craving and relapse, and the effects of anxiety, depression and/or aggressiveness on such interactions in the context of a randomized controlled trial of baclofen for alcohol dependent subjects over 12 consecutive weeks. Forty-two treatment-seeking subjects were randomly assigned to baclofen 10 mg t.i.d. or 20 mg t.i.d. or placebo in a 12-week double-blind placebo-controlled randomized clinical trial. The Timeline Follow Back (TLFB) was used to assess for the number of drinks consumed during the 12-week period, and measurements of blood levels for cortisol and aldosterone were taken. Additional questionnaires were administered to evaluate their craving for alcohol (Penn Alcohol Craving Scale (PACS) and the Obsessive Compulsive Drinking Scale (OCDS) and its two subscales ODS for obsessions and CDS for compulsions, as well as anxiety (State and Trait Inventory (STAI)), depression (Zung Self-Rating Depression Scale (Zung)) and aggression (Aggressive Questionnaire (AQ)). We found the mean cortisol concentration to be significantly lower at week 0 than at week 12 (117.33ng/mL Vs 153.5 ng/mL,  $t=2.58$ ,  $dF=29$ ,  $p=0.015$ ). At week 0, no significant correlations were found between aldosterone or Cortisol and the craving or psychometric scales, however, at week 12, there was a significant correlations between aldosterone levels and the number of drinks consumed when subjects relapse ( $r=0.606$ ,  $p<0.001$ ), as well as with OCDS ( $r=0.439$ ,  $p=0.022$ ), its obsessive subscale ODS ( $r=0.424$ ,  $p=0.027$ ), and its compulsive subscale CDS ( $r=0.414$ ,  $p=0.032$ ), and with STAI-Y1 ( $r=0.422$ ,  $p=0.028$ ). Hormone levels were not found to be different across the three groups (baclofen 10mg t.i.d., 20mg t.i.d., and placebo) either at week 0 or at week 12. Controlling for the medication condition, abstinent subjects had a lower aldosterone level at week 12 (232pg/mL Vs 134 pg/mL,  $F(1,23)=4.3$ ,  $p=0.049$ ). In patients with alcohol dependence

there is a significant correlation between aldosterone, and the amount of alcohol use, craving, and anxiety. If confirmed in larger samples, these findings could be used as biomarkers for the severity of symptoms, and prognosis in alcohol dependence. Mechanistic studies are also needed in order to shed light on the possible mechanisms of action underlying the associations observed here.

### **Learning Objectives:**

- Understanding the role of adrenal cortical hormones in the course of alcohol use disorders.
- Understanding neuropsychoenocrinological effects of baclofen treatment for alcohol use disorders.

**Source of Funding:** The present study was supported by a grant from the European Foundation for Alcohol Research (ERAB) and by ‘Associazione Ricerca in Medicina’ (Rome, Italy).

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### **ADDICTION SEVERITY INDEX FAMILY COMPOSITE SCALE MORE RELIABLE THAN COMBINED FAMILY/SOCIAL COMPOSITE**

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**Specific Purpose:** This poster presents results demonstrating that creating separate Family and Social Composites of the Addiction Severity Index yields scales with higher reliability than the combined Family/Social Composite. **Content:** The Addiction Severity Index is widely used however a review assessing reliability of the ASI composite scores expressed concern about the Family/Social composite score after finding that the composite demonstrated low internal consistencies (Mäkelä, 2004). The Family/Social composite asks about relationships with family, friends, co-workers, and neighbors. It was our opinion that problems with family relationships are often independent of problems with non-family members. Indeed, the EuropASI is a European adaptation of the fifth edition of the ASI (Kokkevi & Hartgers, 1995) which has separate Family and Social composite scores. **Methodology:** Secondary analyses were performed on data from seven studies conducted through the NIDA Clinical Trials Network. Data from each study was analyzed separately. Composites were computed based upon both the traditional ASI scoring and the EuropASI scoring. Factor analysis was used to explore whether the items from the EuropASI Family and Social scales factor as two separate factors. Reliability of the scales was compared using the Feldt test. **Results:** Factor analysis conducted with data from six studies showed factors that correspond to the two factors in the proposed by the EuropASI. The PCA conducted with data from the seventh study revealed three factors; however, these factors still separated the family items from the other social items. Reliability of the EuropASI Family composite ranged from .777 to .867 with mean reliability  $M = .834$ . Reliability of the EuropASI Social composite ranged from .693 to .805 with mean reliability  $M = .757$ . Reliability of the ASI Family/Social Composite Scale ranged from .664 to .758 with mean reliability  $M = .705$ . Across all 7 studies, the EuropASI Family composite had significantly ( $p < .05$ ) higher reliability than the ASI Family/Social Composite. The EuropASI Social composite had significantly ( $p < .05$ ) higher reliability than the ASI Family/Social composite across three studies. **Importance of the Proposed Poster:** The EuropASI Family Composite was more reliable than the Family/Social composite obtained from traditional scoring. In a separate study (Denton, Adinoff, Lewis, Walker, & Winhusen, 2014) we found that pregnant substance users with family discord

(assessed by the EuropASI) reported a higher percentage of substance use days and also had a greater proportion of positive urine drug screens over the four month study period. These results point toward the importance of assessing family functioning using the EuropASI Family composite scoring. References Denton, W. H., Adinoff, B. H., Lewis, D., Walker, R., & Winhusen, T. (2014). Family discord is associated with increased substance use for pregnant substance users. *Substance use & Misuse*, 49(3), 326-332. doi:10.3109/10826084.2013.840002; 10.3109/10826084.2013.840002 Kokkevi, A., & Hartgers, C. (1995). Europe ASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *European Addiction Research*, 1, 208-210.

### **Learning Objectives:**

- Be able to describe the structure of the ASI Family/Composite.
- Be able to explain differences between the EuropASI approach to family and social assessment and the traditional ASI scoring.

**Source of Funding:** None

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### **PERIODIC PLACEBO EFFECT IN AN ADDICTION THERAPY TRIAL**

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**Objective:** To determine whether clinical outcomes vary over the four-week injection cycle with XR-NTX. **Methods:** In opioid-dependent patients who received XR-NTX (N=126) or placebo (N=124) during a 24-week, double-blind, placebo-controlled clinical trial, multivariate regression was used to analyze craving, opioid use and discontinuation with predictor terms for number of injections, time from previous injection, time squared and other interaction terms. We explored craving over time with quadratic and logarithmic trend models, and opioid use and discontinuation using a generalized estimating equation model. **Results:** Craving: Both linear and quadratic effects were significant (both  $p=0.001$ ), with a negative coefficient for the linear term ( $\beta_1 = -3.49$ ) and a positive coefficient for the quadratic term ( $\beta_2 = 0.604$ ), indicating that craving first declines after injection then very slightly rises before the next injection. This effect was not different, however, for XR-NTX vs. PBO ( $p=0.251$ ). Opioid Use and Discontinuation: Time from previous injection was significant (all  $p=0.001$ ), indicating that the longer the time from injection the greater the likelihood of a patient using opioids and discontinuing. These effects were not different, however, for XR-NTX vs. PBO ( $p=0.872$  and  $p=0.478$ , respectively). **Conclusion:** Within the 4-week injection cycle, the observed time course of change in craving, opioid use and discontinuation is not different between XR-NTX vs. PBO. Non-significant interaction means the XR-NTX benefit vs. PBO is consistent over weeks 1-4. The double-blind, RCT design demonstrates that the effect of time is not pharmacologic in nature. These findings underscore the clinical role for psychosocial management with XR-NTX treatment.

### **Learning Objectives:**

- Learn about the periodic placebo effect in an addiction study.

**Source of Funding:** Funded by Alkermes, Inc., Waltham, MA. Injectable extended-release naltrexone (Vivitrol®) was developed with support from National Institute on Drug Abuse Grant R43DA013531 and National Institute on Alcohol Abuse and Alcoholism Grant N43AA001002.

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## **ADRENERGIC RECEPTOR MODULATION FOR THE TREATMENT AND PREVENTION OF POST-TRAUMATIC STRESS DISORDER AND CO-MORBID DISORDERS**

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**Abstract:** A pathophysiological model of posttraumatic stress disorder (PTSD) posits that an overly strong stress response at the time of the traumatic event leads to over-consolidation of the event's memory in part through a central  $\beta$ -adrenergic mechanism. We hypothesized that the presence of a  $\beta$ -blocker in the patient's brain at the time of the traumatic event would reduce the PTSD outcome by blocking this effect. The unpredictable, uncontrollable discharge of an implantable intra-cardiac defibrillator (ICD) is experienced by most patients as highly stressful, and it has previously been shown to be capable of causing PTSD symptoms. The present pilot study evaluated a convenience sample of 18 male cardiac patients who had been taking either a lipophilic  $\beta$ -blocker (which penetrates the blood-brain barrier) or a hydrophilic  $\beta$ -blocker (which does not) at the time of a discharge of their ICD. The self-report PTSD Checklist-Checklist-Specific Version quantified 17 PTSD symptoms pertaining to the ICD discharge during the month preceding the evaluation. There was a statistical trend for patients who had been taking a lipophilic  $\beta$ -blocker at the time of the ICD discharge to have (35%) less severe PTSD symptoms than patients who had been taking a hydrophilic  $\beta$ -blocker (one-tailed  $p=0.07$ ,  $g=0.64$ ). Further, prospective, randomized, controlled studies are suggested. In addition, an expansion of these findings to other PTSD populations as well as other disorders with an increased attention bias to threat, exaggerated startle, or other physiological biomarkers of impaired fear extinction (including bipolar disorder and schizophrenia) could also be explored in future pilot studies. Currently the applicant is a NARSAD 2013 Young Investigator grantee exploring a beta-blocking, nicotinic antagonist treatment for PTSD using a memory re-activation/ disruption of consolidation protocol. She has also submitted for U Mass Pilot Project Program funding with research mentor Dr. A Anthony Rothschild to study attention bias to threat as a biomarker in bipolar I and potential therapeutic target to lower mood episode recurrence risk.

### **Learning Objectives:**

- To understand the mechanisms of impaired fear extinction and memory over-consolidation (mediated by neuroendocrine and catecholamine signaling) that underlie PTSD and other stressor-related disorders.
- To consider novel drugs with beta- and adrenergic-blocking activity (such as carvedilol, metoprolol and others) as novel PTSD therapeutics as well as potential treatments for stress-related symptoms of other disorders.

**Source of Funding:** R-01 Administrative Supplement to MH068603

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## **AN EPIGENOME-WIDE ASSESSMENT OF ATYPICAL ANTIPSYCHOTIC SIDE EFFECTS IN BIPOLAR DISORDER**

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**Background:** Atypical antipsychotic (AAP) use has become increasingly common over the past 10 years in both the acute and maintenance phases for patients with bipolar disorder, which has brought with it an increase in cardiovascular mortality. While many different risk factors are thought to be at the root of this medication related adverse event, such as diet, sedentary lifestyle and genetics, little work has been done to examine the interaction between all of these risk factors. Investigating AAPs' effects on DNA methylation or, pharmacoepigenetics, incorporates the effect of the environment on genetic manipulation and may allow for identification of new biomarkers for AAP metabolic side effects. How AAPs influence DNA methylation in bipolar subjects is currently unknown. Our group has previously reported that bipolar subjects treated with AAPs carrying the highest risk for metabolic side effects have low global DNA methylation using the LUMInometric Methylation Assay (LUMA). Therefore the aim of this investigation was to examine differences in global DNA methylation in bipolar subjects treated with AAPs or lithium monotherapy using the Illumina 450K BeadChip. **Methods:** DNA was collected as part of a larger study assessing metabolic syndrome in bipolar disorder. All subjects (n = 96) had clinical and fasting metabolic measurements taken within 3 hours of their normal waking time. Subjects also underwent a brief dietary and exercise assessment. Bipolar disorder diagnosis was verified by a structured clinical interview and medical chart review. Illumina 450K data was preprocessed using several bioinformatics strategies including: 1) removal of poor quality probes, 2) removal of SNPs found on array, 3) probe-to-probe normalization and 4) batch normalization. Subjects were grouped based on Lithium or AAP use and compared using R statistical software packages and controlling for age, gender, diet and exercise. **Results:** Of the 96 bipolar subjects included, 66 were on AAPs and 30 were on lithium monotherapy. The average age was 44.9±11.2 years, 62.5% were female and 90% were Caucasian. The AAP group had significantly higher rate of metabolic syndrome diagnosis compared to the lithium group (56% vs. 27%). No other significant demographic differences between the groups were found. No samples were removed after reviewing data quality from array. Preliminary results have identified a probe contained within the Protein Tyrosine Phosphatase Receptor Type N Polypeptide 2 (PTPRN2) gene that was hypomethylated in the AAP population (corrected p-value = 0.02) compared to those receiving lithium. This gene is associated with autoantibody production in type I diabetes. Analysis is ongoing and future work will investigate differentially methylated regions based on treatment type. **Conclusions:** This work is the first to investigate DNA methylation of bipolar subjects based on AAP use. We have identified a potential target in a gene associated with aberrant glucose regulation in type I diabetes. Future work will be to identify the top 5 differentially methylated regions of interest and use these results to look at gene methylation more in depth at the single nucleotide level. Identification of a new biomarker linked to AAP metabolic side effects in bipolar disorder is exciting and important as it may lead to personalized medicine therapy and therapy targeted at treating the altered methylation seen in a particular gene (e.g., methyl-donor therapy).

### **Learning Objectives:**

- Understand the implications of using atypical antipsychotics in bipolar disorder.
- Explain pharmacoepigenetics and its utility in studying medication side effects.

**Source of Funding:** 1) The University of Michigan Depression Center - Rachel Upjohn Clinical Scholars Pilot Grant 2) NIH Grant 5R01MH082784-04 3) The National Alliance for Research in Schizophrenia and Depression (NARSAD) 4) The Prechter Longitudinal Study

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## **BIOMARKERS OF CARDIOMETABOLIC RISK IN ANTIPSYCHOTIC TREATED YOUTH**

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**Background:** The metabolic consequences of obesity have rapidly become a major public health concern in US youth, (1) with evidence that children with mental health conditions may be at particular risk. (2) The identification of proximate biomarkers of metabolic risk for use as surrogate endpoints in treatment studies can address this problem. Changes in CIMT are positively correlated with metabolic syndrome criteria in otherwise healthy youth. (3) Magnetic Resonance Spectroscopy (1H MRS) measuring HTGC is a surrogate measure of steatohepatitis, the most common liver abnormality found in children. (4) **Methods** Participants were antipsychotic-treated youth ages 6-19 and healthy controls, matched across a range of BMI %ile. Metabolic Assessments included plasma analysis of fasting glucose, insulin and lipids, as well as fibrinogen, high-sensitivity C-reactive protein (hs-CRP) and liver enzymes. CIMT was measured with 9-MHz B-mode ultrasonography; HTGC was measured with 1H MRS of the liver; body composition was measured via Dual Energy X-Ray Absorptiometry (DEXA). Analysis of Covariance (ANCOVA) and multiple stepwise regression was used to identify separate best fit models for the prediction of CIMT and HTGC values. **Results** A total of 43 children, mean age 11.5 (SD 2.9, SE=0.4) years participated in the study (antipsychotic treated n=24, healthy controls n=19). There were no significant differences between groups on the primary outcome measures. In the pooled group, DEXA total % fat explained the majority of the variance in both CIMT (34%) and HTGC (30%). BMI%ile accounted for 30.4% of the variance in CIMT and 15.2% of the variance in HTGC. Waist circumference accounted for 38.1% of the variance in CIMT and 17.4% of the variance in HTGC. Plasma indicators of metabolic risk contributed to explanation of variance in both measures, but to a lesser degree. **Conclusions** These results suggest that adiposity, waist circumference and BMI%ile are strong predictors of an adverse metabolic risk profile in all youth, regardless of antipsychotic treatment status. Further prospective study utilizing such proximal indicators of risk is needed to characterize the development of risk conditions during treatment and to describe risk at the highest levels of adiposity where clinical indicators may be less useful.

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### **Learning Objectives:**

- Participants will learn how gold standard metabolic biomarkers can sensitively identify and track developing metabolic dysfunction in youth treated with antipsychotic medications.
- Participants will learn how clinically-available measures of metabolic dysregulation, like BMI%ile and fasting plasma measures, correlate with gold-standard biomarkers.

**Source of Funding:** This research was supported by a Brain & Behavior Foundation (formerly known as NARSAD) Young Investigator Award and by the Sidney R. Baer, Jr. Foundation.

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### **PLASMA POLYUNSATURATED FATTY ACID MARKERS DIFFER IN SYMPTOMATIC BIPOLAR DISORDER**

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**Introduction:** Post-mortem brain studies in bipolar disorder (BD) have shown elevated markers of the pro-inflammatory omega-6 polyunsaturated fatty acid (PUFA) arachidonic acid (AA) cascade. In animal models, clinically effective mood stabilizers down regulate the AA cascade, while similar medications that are not clinically effective mood stabilizers do not. Further, antidepressants that increase the frequency of switching in BD upregulate rat brain AA metabolism, suggesting higher metabolism in mania than in depression. We hypothesized that plasma levels of fatty acid markers would differ between symptomatic BD patients and healthy controls (HC). **Methods:** We recruited symptomatic BD subjects and HC for diagnostic interviewing, mood rating scales, measurement of sleep quality, and obtained blood and saliva samples. We measured plasma unesterified and esterified concentrations of 8 fatty acids in 17 BD and 18 HC subjects. Plasma concentrations between groups were compared using Mann-Whitney U tests. For the fatty acids that differed between groups, relations between symptom scales, BMI, antipsychotic treatment and fatty acid concentrations were compared using Spearman's rho. **Results:** Mean age was similar between groups (in years: BD 35.9 +/- 10.9, HC 32.4 +/- 11.3; p=0.36), but mean BMI was significantly higher in the BD group (in kg/m<sup>2</sup>: BD 31.3 +/- 5.6, HC 24.8 +/- 3.8, p<0.001). The mean Hamilton Depression Rating Scale score for the BD group was 29.1 +/- 14.6, Young Mania Rating Scale score was 13.6 +/- 11.5. The median plasma level of esterified palmitoleic acid was significantly higher in BD than HC (BD 161 nmol/mL, HC 116 nmol/mL; p=0.04), and median plasma levels of esterified ALA was higher in the BD group at a marginally significant level (BD 13 nmol/mL, HC 10 nmol/mL; p=0.08). The median ratio of unesterified:esterified ALA was lower in BD (p=0.04). The median ratio of unesterified DHA:ALA was higher in BD than HC (p=0.02), but the median ratio of esterified DHA:ALA was lower in BD (p=0.02), and was negatively correlated with BMI in BD (-0.538, p=0.03). The mania score was inversely correlated with unesterified DHA:ALA at the trend level (-.466, p=0.06), and depressive scores were correlated with esterified palmitoleic acid (0.523, p=0.04). Treatment with antipsychotics was not associated with any of the FAs (p>0.10).

Discussion: Several plasma fatty acid concentrations differed between BD and HC. Unesterified polyunsaturated fatty acids cross the blood-brain barrier, and differences in the plasma ratios of unesterified to esterified species may indicate abnormalities in availability that could affect brain functioning. Though pre-clinical studies indicate that the PUFA system is important in BD, clinical studies of n-3 PUFA supplementation have been mixed. Different approaches are needed to determine whether alteration of brain PUFA metabolism by diet or drugs will be an effective treatment for BD. References: Kim HW, Rapoport SI, Rao JS. Altered arachidonic acid cascade enzymes in postmortem brain from bipolar disorder patients. *Mol Psychiatry*. 2011;16(4):419-28. Rapoport SI, Basselin M, Kim HW, Rao JS. Bipolar disorder and mechanisms of action of mood stabilizers. *Brain Res Rev*. 2009;61(2):185-209.

### **Learning Objectives:**

- Markers of the polyunsaturated fatty acid system may differ in bipolar disorder.
- Alteration of the polyunsaturated fatty acid system may be a therapeutic target in bipolar disorder.

**Source of Funding:** The project described was supported by the National Center for Research Resources, Grant KL2 RR033180, and is now at the National Center for Advancing Translational Sciences, Grant KL2 TR000126. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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### **RELIABLE CHANGE INDEX AND CLINICAL SIGNIFICANCE IN CLINICAL TRIALS USING THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)**

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Background: The PANSS is the most widely used measures of psychopathology in schizophrenia. It is commonly used in both randomized controlled trials (RCT) and non-controlled evaluations. RCTs assess clinical efficacy of an intervention relative to a placebo or control condition by making group comparisons and evaluating for statistically significant differences. However, statistical significance does not in itself provide concise information about a given intervention's clinically meaningful effects. The process of defining clinical significance remains a challenge. As an attempt to develop a standard method of estimating clinically significant change, we propose adoption of a two-part strategy: The first part of the strategy involves using the Reliable Change Index (RCI). The second part involves use of examination of clinical significance (CS). RCI is whether patients changed sufficiently that the change is unlikely to be due to measurement unreliability. CS change takes the patient from a score typical of schizophrenia to a score typical of the "normal" population. Studying RCI and CS has moved the outcomes paradigm from studying treatment groups to studying individual change within those groups. Assessments must move beyond symptom focus and evaluate individuals with respect to the complex broader domains of their functional, real-world, lives in which clinically significant change is operationalized. To provide a comparison of concepts and analysis of clinical significance (CS) and the reliable change index (RCI) using pre and post PANSS scores. Methods: Data on symptomatology, PANSS, from CATIE were analyzed. Three methods of RCI (Jacobson-Truax, Edwards-Nunnally, and Hageman-Arindell methods) were compared to CS

change (pre to post change of at least 2 SDs from the original mean, 20% improvement, and change in PANSS remission criteria). Results: For the three RCI methods, 29.73%, 31.08% and 52.70% showed reliable improvements in PANSS scores. For CS, 22.97% showed greater than 20% improvement, 29.73% improved on the PANSS remission criteria, and only 8.11% showed CS improvement of 2 SDs from the mean. When comparing RCIs with CS, only 18.92% of CS improvement also resulted in RCI significant improvement. Regarding clinically meaningful improvement, the Hageman-Arindell method was most concordant with all three RCI measures and with the 20% improvement as this method differentially analyzes clinically meaningful change at the individual level and at the group level (i.e., obtaining proportions of patients who have reliably changed and passed the cutoff point). Conclusions: Reliable and clinically significant change should be reported in articles to complement the more familiar group summary methods. Assessment of clinically meaningful change is useful for evaluating treatment response. Outcome studies often assess statistically significant change, which may not be clinically meaningful. Comparisons of the proposed methods of determining clinically significant PANSS outcomes to biomedical standards of clinical significance will help determine the validation of this procedure, and improve the precision and effectiveness of the PANSS in clinical trials.

### **Learning Objectives:**

- The audience will learn how reliable and clinically significant change should be reported in articles to complement the more familiar group summary methods.
- The audience will learn how the difference between statistically significant change, which may not be clinically meaningful.

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## **PRENATAL STRESS EVOKES LONG-TERM CHANGES IN BRAIN GLUCOSE METABOLISM**

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*Polish Academy of Sciences*

Objectives Clinical and pre-clinical studies show that adverse factors acting during perinatal period may cause developmental abnormalities and increase susceptibility to a variety of diseases (Tarry-Adkins and Ozanne, 2011). Most evidence suggests that increased glucocorticoid action can evoke long-term metabolic, endocrine and behavioral changes which may be responsible for the development of depression in later life. Impairment of brain glucose metabolism is a possible link between stress and disturbances leading to manifestation of depression (Hryhorczuk et al., 2013). However apart from an increase in blood glucose and a decrease in insulin signaling in the hypothalamus in animal models of depression, there are no data about the glucose concentrations or metabolism in brain regions that are important in the pathogenesis of depression. The aim of the present study was to evaluate glucose concentrations and metabolism in the hippocampus and the frontal cortex of rats that had been subjected to prenatal stress, which is a commonly accepted animal model of depression. Glucose metabolism was determined under basal conditions and in animals that have been subjected to stress in adulthood and after the administration of glucose. Method Pregnant Sprague-Dawley rats were exposed to three stress sessions per day from 14th to 21st day of pregnancy. After weaning, male rats were housed for 3 months and next the Porsolt test was performed. Some animals were exposed to acute immobility

stress while other rats received glucose. The animals were killed by decapitation and the brain structures were rapidly dissected. Glucose, glucose transporters and selected glycolytic and aerobic respiration enzymes were determined. Result It was found that prenatally stressed rats had significantly higher levels of immobility behavior in the Porsolt test than control animals, i.e. they showed depression-like behavior. Prenatal stress increased glucose concentration, glucose transporters and concentration of some glycolytic enzymes but decreased the levels of aerobic respiration enzymes. These changes were greater in stress or glucose loaded animals than under the basal condition. Conclusion The obtained results indicate that prenatal stress increases glucose concentration in the hippocampus and frontal cortex. The elevated glucose levels in these brain structures are likely to result from changes in the levels of glucose transporters, especially GLUT1. The stimulation of the glycolytic processes appears to be a compensatory mechanisms that responds to the inhibition of aerobic respiration. Moreover, the obtained results support the hypothesis that stress during the perinatal period permanently increases the sensitivity of brain tissue to adverse factors that act in adult animals.

### Learning Objectives:

- Hryhorczuk C., Sharma S., Fulton S.E.: Metabolic disturbances connecting obesity and depression. *Front. Neurosci.*, 2013, 7, 177. eCollection.
- Tarry-Adkins J.L., Ozanne S.E.: Mechanisms of early life programming: current knowledge and future directions. *Am. J. Clin. Nutr.*, 2011, 94(6 Suppl), 1765S-1771S.

**Source of Funding:** Acknowledgements This work was supported by the Operating Program of Innovative Economy 2007-2013, grant No. POIG.01.01.02-12-004/09.

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### **EFFICACY AND SAFETY OF TREATMENT WITH LURASIDONE ADJUNCTIVE WITH LITHIUM OR VALPROATE IN BIPOLAR I DEPRESSION: RESULTS OF TWO 6-WEEK STUDIES**

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**Introduction:** Few studies have been reported that demonstrate the efficacy of adjunctive therapy for patients with bipolar I depression who have had an insufficient response to monotherapy with mood stabilizing agents. (1,2). Currently, lurasidone is the only atypical antipsychotic approved by the FDA for adjunctive therapy of bipolar I depression with lithium (Li) or valproate (VPA; 3). The aim of the current analysis was to evaluate the efficacy and safety of adjunctive therapy with lurasidone in bipolar I depression utilizing pooled data from 2 studies. **Method:** Data were pooled from 2 studies in which patients meeting DSM-IV-TR criteria for bipolar I depression received 6 weeks of double-blind treatment with lurasidone 20-120 mg/day (N=355) or placebo (N=327), adjunctive with Li or VPA. The primary and key secondary efficacy measures were, respectively, the Montgomery Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression Bipolar Severity of Illness (CGI-BP-S), analyzed by MMRM. Secondary efficacy outcomes included the Quick Inventory of Depressive Symptomology – Self Report (QIDS-SR16), Hamilton Anxiety Rating Scale (HAM-A), and Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q). **Results:** At week 6 endpoint, treatment with lurasidone

(vs. placebo) was associated with improvement vs. placebo in the mean MADRS (-14.4 vs. -11.9;  $p=0.003$ ), CGI-BP-S (-1.7 vs. -1.3;  $p=0.001$ ), QIDS-SR16 (-7.4 vs. -5.7;  $p\leq 0.001$ ), HAM-A score (-7.0 vs. -5.0;  $p\leq 0.001$  [LOCF]), and Q-LES-Q (+18.5 vs. +13.2;  $P<0.001$ ). Responder rates (MADRS reduction  $\geq 50\%$ ) were significantly higher with lurasidone vs. placebo (48% vs. 37%;  $p=0.002$ ; LOCF-endpoint). Minimal LOCF-endpoint changes were observed for adjunctive lurasidone vs. placebo in mean weight (+0.1 vs. +0.2 kg), median total cholesterol (-4.0 vs. -1.0 mg/dL), LDL (-3.0 vs. -1.0 mg/dL), triglycerides (+4.0 vs. -2.0 mg/dL), and glucose (0.0 vs. 0.0 mg/dL). Discontinuation rates due to adverse events were similar for lurasidone vs. placebo (5.8% vs. 4.8%); adverse events ( $\geq 5\%$  incidence) were nausea (13.9% vs. 10.2%), Parkinsonism (12.8% vs. 8.1%), somnolence (11.4% vs. 5.1%), and akathisia (10.8% vs. 4.8%). Conclusions: Results of this pooled analysis demonstrated that adjunctive therapy with lurasidone and Li or VPA was effective in treatment of patients with bipolar depression, with a low rate of discontinuation due to adverse events and minimal effect on weight or metabolic parameters.

### References:

- Sachs GS, Ice KS, Chappell PB, et al. Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder. *J Clin Psychiatry* 2011;72:1413-22.
- Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. *CNS Spectr* 2013;18:199-208.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as Adjunctive Therapy With Lithium or Valproate for the Treatment of Bipolar I Depression. *Am J Psychiatry* 2014;171:169-177

### Learning Objectives:

- At the completion of this session participants will be able to demonstrate knowledge of the efficacy of lurasidone adjunctive therapy with lithium or valproate for the treatment of bipolar depression.
- At the completion of this session participants will be able to demonstrate knowledge of the safety of lurasidone adjunctive therapy with lithium or valproate for the treatment of bipolar depression, including its effects on weight and metabolic parameters.

**Source of Funding:** Sunovion Pharmaceuticals Inc.

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### **MOODSWINGS 2.0 (WWW.MOODSWINGS.NET.AU): AN ONLINE INTERVENTION FOR BIPOLAR DISORDER**

*Victoria E. Cosgrove<sup>1</sup>, Trisha Suppes<sup>1</sup>, Sue Lauder<sup>2</sup>, Emma Gliddon<sup>3</sup>, Karishma Raju<sup>4</sup>, Seetal Dodd<sup>3</sup>, E. Grace Fischer<sup>5</sup>, Michael Berk<sup>3</sup>*

*<sup>1</sup>Stanford University School of Medicine, <sup>2</sup>University of Melbourne, <sup>3</sup>Deakin University, <sup>4</sup>VA, Palo Alto, <sup>5</sup>VA Palo Alto Healthcare System*

Background: The application of adjunctive psychosocial interventions in bipolar disorder is often limited in real world application due to cost and access constraints. MoodSwings 1.0 was a pilot online self-help program for people with bipolar disorder adapted from a validated group-based face-to-face program. MoodSwings 1.0 compared the online delivery of MoodSwings (interactive tools plus psychoeducation) with psychoeducation alone, using the same platform and both with access to small group moderated discussion boards. Participants diagnosed with

bipolar I or II disorder (n = 156) were randomised to either online programs of MoodSwings 1.0 or psychoeducation. Improvement in both groups showed baseline to endpoint reductions in mood symptoms and improvements in quality of life, functionality, and medication adherence. MoodSwings was noted to be superior to psychoeducation in improvement on symptoms of mania at 12 months (p=0.02). MoodSwings 2.0 was developed in response to these promising findings. Method: Participants diagnosed with bipolar I,II or NOS will be recruited. MoodSwings 2.0 is a 2-site, 3-arm randomized parallel group stepped design (exposure to moderated peer discussion board only, discussion board only, discussion board plus psychoeducation or discussion board, psychoeducation, and online interactive psychosocial tools. The collaborative sites (Palo Alto, CA, and Melbourne, Australia) will enroll 300 participants internationally. Outcomes will be assessed at quarterly intervals via phone interview with raters blind to group assignment as well as online self-report. Results and discussion: The primary outcome of MoodSwings 2.0 will be the change in depressive symptoms over 12 months, assessing if there is additive benefit to the three components (education, discussion board, and interactive psychosocial tools) on improvement. Exploratory aims include symptoms of elevated mood, health services utilization, evidence of relapse (time to intervention), function, quality of life and medication adherence. Conclusion and future directions: Experience of the MoodSwings 1.0 trial study suggests that internet-based psychosocial interventions have potential in the management of bipolar disorder. Online enhancements in MoodSwings 2.0, as well as a larger sample size including an attention control (discussion board only arm) may lead to a greater understanding of these interventions as an adjunctive treatment tool.

#### **Learning Objectives:**

- To introduce the background and methodology of MoodSwings 2.0 as a viable adjunctive treatment option for individuals with bipolar disorder.
- To provoke thought and discussion about what treatment components of an online intervention may be most effective for individuals with bipolar disorder seeking adjunctive care.

**Source of Funding:** National Institute of Mental Health, R34 MH091284

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#### **CLINICALLY RELEVANT CHANGE USING CGI-BP IN PATIENTS WITH ACUTE DEPRESSIVE EPISODES OF BIPOLAR I OR II DISORDER IN QUETIAPINE XR STUDY**

*Catherine Datto, Jason Wright, Scott LaPorte, Michelle Shay*

*AstraZeneca*

Introduction: Clinical studies of major depressive episodes designed to meet requirements for regulatory approval often include the Montgomery-Åsberg Depression Rating Scale (MADRS) as a primary outcome measure. This scale requires rater training and is not used in routine clinical practice. Another scale often included in clinical trials that may have more relevance for clinical practice is the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP). This scale does not require rater training and uses clinically intuitive questions. The clinician asks one question in each of the Overall, Depression, and Mania domains on a patient's clinical severity (CGI-BP-S) or change since starting treatment (CGI-BP-C).(1) Methods: This was a double-blind, randomized, placebo-controlled study of quetiapine XR (300 mg daily) in adults with a clinical diagnosis of bipolar I or II disorder and acute depressive episodes (HAM-D-17

score  $\geq 20$  and HAM-D item 1 [depressed mood] score  $\geq 2$ ). (2) Primary endpoint was the efficacy of quetiapine XR vs placebo measured by MADRS score change from baseline to Week 8. Secondary variables were CGI-BP-S and CGI-BP-C. Adverse events were recorded throughout the study. Results: 280 patients were randomized to treatment. Least squares mean (SE) change in MADRS score from baseline was -17.43 (1.24) for quetiapine XR and -11.92 (1.18) for placebo ( $P < 0.001$ ) at Week 8, and -10.16 (0.91) vs -6.54 (0.87) ( $P < 0.001$ ) at Week 1. Mean difference in change in CGI-BP-S Overall for quetiapine XR vs placebo was -0.57 (0.16) ( $P < 0.001$ ) at Week 8, and -0.35 (0.10) ( $P < 0.001$ ) at Week 1. Mean difference in change in CGI-BP-S Depression for quetiapine XR vs placebo was -0.64 (0.16) ( $P < 0.001$ ) at Week 8, and -0.36 (0.10) ( $P < 0.001$ ) at Week 1. Mean difference in CGI-BP-C for quetiapine XR vs placebo was -0.53 (0.15) ( $P < 0.001$ ) at Week 8, and -0.45 (0.11) ( $P < 0.001$ ) at Week 1. Mean difference in CGI-BP-C Depression for quetiapine XR vs placebo was -0.54 (0.15) ( $P < 0.001$ ) at Week 8, and -0.46 (0.11) ( $P < 0.001$ ) at Week 1. The Mania domain showed little change, as expected in this acute depression study, with few switches to mania as defined by YMRS score. Quetiapine XR as monotherapy in patients with acute depressive episodes of bipolar I or II disorder was generally well tolerated and demonstrated no new safety findings. Conclusion: CGI-BP detected clinical improvements with quetiapine XR vs placebo at 8 weeks and as early as Week 1, as did the MADRS score. CGI-BP-S and CGI-BP-C may be more clinically meaningful and easier for clinicians to use than the MADRS in patients with acute depressive episodes associated with bipolar I or bipolar II disorder.

#### References:

- Spearing MK, Post RM, Leverich GS, et al. *Psychiatry Res.* 1997;73:159-71.
- Suppes T, Datto C, Minkwitz M, et al. *J Affect Disord.* 2010;121:106-15.

#### Learning Objectives:

- At the conclusion of this presentation, the participant should be able to demonstrate knowledge and understanding of the utility of CGI-BP-S and CGI-BP-C to assess patients with acute depressive episodes of bipolar I or II disorder treated with once-daily quetiapine XR.
- At the conclusion of this presentation, the participant should appreciate that the benefit of quetiapine XR over placebo can be seen as early as Week 1 using either scale, and continued through Week 8.

**Source of Funding:** AstraZeneca

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### **NUMBER NEEDED TO TREAT FOR DISCONTINUATION DUE TO ADVERSE EVENTS, SOMNOLENCE, $\geq 7\%$ WEIGHT GAIN, EXTRAPYRAMIDAL SIDE EFFECTS, RESPONSE, AND REMISSION OF ATYPICAL ANTIPSYCHOTICS IN ACUTE BIPOLAR DEPRESSION**

*Keming Gao*

*Case Western Reserve University*

Background: Three atypical antipsychotics have been approved by the FDA for acute treatment of bipolar depression. Due to an unmet need for acute bipolar depression, the off-label use of other atypical antipsychotics and other pharmacological agents in bipolar depression is

inevitable. The aim of this analysis was to estimate the number needed to treat (NNT) for the discontinuation due to adverse events (DAEs), common side effects including somnolence,  $\geq 7\%$  weight gain, overall extrapyramidal side effects, and akathisia, response, and remission of atypical antipsychotics, lithium, paroxetine, and lamotrigine relative to placebo in the acute bipolar depression. Methods: English-language literature published and cited in Medline was searched with terms of atypical antipsychotic/generic and brand names of atypical antipsychotics, bipolar depression/bipolar disorder, and randomized, placebo-controlled trial. The data of DAEs, somnolence,  $\geq 7\%$  weight gain, overall EPS (extrapyramidal side effects), akathisia, response defined as  $\geq 50\%$  improvement on MADRS (Montgomery-Asberg Depression Rating Scale) total score, and remission defined as  $\leq 12$  or 8 on MADRS total score were extracted from original publications. The NNT for these variables of active treatments relative to placebo was estimated and presented with the mean and 95% confidence interval. Results: Olanzapine monotherapy, the combination of olanzapine and fluoxetine (OFC), quetiapine-IR monotherapy, quetiapine-XR monotherapy, lurasidone monotherapy and lurasidone adjunctive therapy were superior to placebo with NNTs for response of 11-12, 4, 7-8, 4, 4-5, and 7, respectively and NNTs for remission of 11-12, 4, 5-11, 7, 6-7, and 6, respectively. There was no significant difference between OFC and lamotrigine, aripiprazole, ziprasidone, lithium, or paroxetine and placebo in response and remission. . Olanzapine monotherapy quetiapine-IR, quetiapine-XR, aripiprazole, and ziprasidone 120-160 mg/d had significantly increased risk for DAEs with NNTs of 24, 8-14, 9, 12, and 10, respectively. With the exception of aripiprazole and lurasidone, all other antipsychotics had significantly increased risk for somnolence with quetiapine-XR having the smallest NNT of 4 and OFC having the largest NNT of 12. Olanzapine monotherapy, OFC, quetiapine-IR and -XR had significantly increased risk for  $\geq 7\%$  weight gain with NNTs of 5, 5, 14, and 20-27, respectively. The NNTs for overall EPS were 15 for lurasidone monotherapy 80-120 mg/d, 19 for aripiprazole, 19-20 for quetiapine-IR, and 23 for lithium. The NNTs for akathisia were 5 for aripiprazole, 12-18 for lurasidone monotherapy, and 38 for ziprasidone monotherapy 120-160 mg /day. Conclusion: The efficacy and safety of atypical antipsychotics in bipolar depression varied widely. Among the FDA approved agents including OFC, quetiapine-IR and-XR, lurasidone monotherapy and adjunctive therapy to a mood stabilizer, the differences in the NNTs for response and remission were small, but the differences in tolerability and common side effects were large, suggesting that selecting an FDA approved atypical antipsychotic for bipolar depression should be based on the safety and tolerability.

### **Learning Objectives:**

- Able to understand the differences in safety and efficacy among the commonly used pharmacological treatments for acute bipolar depression.
- Able to understand the clinical relevance of the outcome measures in clinical trials.

**Source of Funding:** none

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### **LURASIDONE IN BIPOLAR I DEPRESSION: A 24 WEEK, OPEN-LABEL EXTENSION STUDY**

*Terence Ketter<sup>1</sup>, Kaushik Sarma<sup>2</sup>, Robert Silva<sup>2</sup>, Hans Kroger<sup>2</sup>, Josephine Cucchiaro<sup>2</sup>, Antony Loebel<sup>2</sup>*

<sup>1</sup>Stanford University School of Medicine, <sup>2</sup>Sunvion Pharmaceuticals, Inc.



**Introduction:** Bipolar disorder is a chronic, recurrent illness, and long-term treatment is complicated by recurrent depressive episodes that predominate over manic episodes in the majority of patients (1). Few agents (quetiapine, lamotrigine) have demonstrated maintenance efficacy in the prevention of depression relapse (2). Lurasidone has demonstrated efficacy in the acute treatment of bipolar depression. The aim of the current study was to evaluate the longer-term safety, tolerability, and effectiveness of lurasidone in bipolar I depression. **Methods:** Patients completing 6 weeks of double-blind, placebo-controlled treatment with either lurasidone monotherapy (1 study) or lurasidone adjunctive therapy with lithium (Li) or valproate (VPA; 2 studies), were treated for 6 months with flexible doses of lurasidone, 20-120 mg/d in this open-label extension study (N=813; monotherapy, 39%; adjunctive therapy, 61%). Safety endpoints were analyzed as change from double-blind baseline to month 6 (observed case analysis). Efficacy endpoints were secondary, and included the MADRS. **Results:** A total of 68% of patients completed the extension study. Adverse events (incidence  $\geq 5\%$ ) for the monotherapy and adjunctive therapy groups, respectively, were 6.0% and 9.5% for akathisia, 11.1% and 5.6% for headache, 7.3% and 7.8% for nausea, 6.3% and 6.4% for insomnia, and 4.4% and 6.6% for anxiety; and 7.0% and 8.7% discontinued due to an AE. Mean change in weight at month 6, for the monotherapy and adjunctive therapy groups, respectively was +0.45 kg and +0.90 kg; and median change was 0.0 mg/dL and -1.5 mg/dL for total cholesterol, +6.0 mg/dL and +8.0 mg/dL for triglycerides, 0.0 mg/dL and +1.0 mg/dL for glucose, and +1.3 mg/dL and +1.3 mg/dL for prolactin. The incidence of treatment-emergent mania was 1.3% in the monotherapy treatment subgroup and 3.8% in the adjunctive subgroup. Mean change on the MADRS, from open-label baseline to month 6, was -6.9 in the monotherapy group and -6.5 in the adjunctive therapy group (observed case analysis). **Conclusions:** Six months of treatment with lurasidone 20-120 mg/d was safe and well tolerated with minimal effect on weight and metabolic parameters. There were minimal differences in tolerability or safety outcomes in patients who received lurasidone monotherapy or adjunctive therapy with lithium or valproate. Treatment with lurasidone was associated with sustained improvement in MADRS.

#### **References:**

- Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord.* 2007;9:531-5.
- Vieta E, Valentí M. Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. *CNS Drugs* 2013;27:515-29.

#### **Learning Objectives:**

- At the completion of this session participants will be able to demonstrate knowledge of the safety and tolerability of lurasidone in the long-term treatment of bipolar depression.
- At the completion of this session participants will be able to demonstrate knowledge of the efficacy of lurasidone for the treatment of bipolar depression.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals Inc.

<sup>1</sup>University of Pittsburgh, <sup>2</sup>University of Pittsburgh School of Medicine

**Objective:** Sleep disturbances are among the most common correlates of bipolar disorder (BP). They contribute to episode onset and recurrence, and are associated with adverse outcomes.(1) Recent work has also suggested that sleep and circadian processes are causally involved in BP.(2) Still, there is a dearth of information on sleep patterns across the spectrum of BP subtypes. We sought to characterize the sleep disturbances of patients with BP I, II, and NOS, and to compare these sleep patterns among diagnostic subtypes of BP and across levels of depression. **Methods:** Participants diagnosed with BP I (n=113), II (n=32) and NOS (n=12) were selected from three clinical trials. Participants completed one week of subjective (sleep diary) and objective (actigraphy) measures of sleep and rest-activity rhythms in the first 10 weeks of treatment. ANOVAs and regression analyses were used to compare sleep across diagnostic subtypes and between levels of depression, and to determine whether group status was associated with each sleep parameter. Two depression groups were created based on a median split of the 25-item Hamilton Rating Scale for Depression scores (HRSD-25(3)) after excluding sleep-related items. Inclusion criteria for the 3 trials differed such that those with BP I were euthymic and obese/overweight at entry and those with BP II and NOS were depressed at entry. As such, depression level and BMI were controlled for in analyses comparing sleep across diagnostic subtypes. **Results:** Sleep and rest-activity patterns were characterized for the participants who completed sleep diary (n=152) and actigraphy (n=145). The three diagnostic groups differed on variables related to sleep timing, duration, and efficiency (SE), with the BPNOS group demonstrating the most delayed sleep times, the shortest sleep duration, and the lowest SE. The vast majority of these differences remained in regression analyses controlling for BMI and for level of depression severity. The two depression groups differed on only two sleep parameters: sleep onset latency (SOL) and SE. The more depressed group demonstrated longer SOL and lower SE only when considering actigraphy-based measures. **Conclusions:** Meaningful differences in sleep patterns exist across BP subtypes. Individuals diagnosed with BPNOS demonstrate the most delayed sleep, shorter sleep duration, and lower SE. One important limitation is the lack of even distribution of depression severity in each diagnostic group. Future work should continue to explore differences in sleep across the BP spectrum using samples that have a similar distribution of depression levels across diagnostic subtypes, and that address the potential effect of mood stabilizing medication and benzodiazepines on sleep. These findings may help to guide appropriate treatment for disturbed sleep among patients with BP.

#### **References:**

- Harvey, A.G. (2008). Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *American Journal of Psychiatry*, 165, 820-829.
- Murray, G., & Harvey, A.G. (2010). Circadian rhythms and sleep in bipolar disorder. *Bipolar Disorders*, 12(5), 459-472.
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, & Psychiatry*, 23, 56-62.

#### **Learning Objectives:**

- To understand the sleep disturbances experienced by individuals with BP I, II, and NOS disorders.
- To examine differences in sleep disturbances across diagnostic subtypes and between levels of depression severity.

**Source of Funding:** 1. NIMH Grant MH081003 2. Depression and Bipolar Disorder Alternative Treatment Foundation Award 3. Lazovik and Huey Awards, Department of Psychology, University of Pittsburgh 4. Drs. Raymond A. and Rosalee G. Weiss Research and Programs Innovation Grant, American Psychological Foundation

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## **GLOBAL IMPROVEMENT IN BIPOLAR MANIA PATIENTS TREATED WITH CARIPRAZINE**

*Robert E. Litman<sup>1</sup>, Kaifeng Lu<sup>2</sup>, Krisztián Nagy<sup>3</sup>, István Laszlovszky<sup>3</sup>, Suresh Durgam<sup>2</sup>*

*<sup>1</sup>CBH Health LLC, <sup>2</sup>Forest Research Institute, <sup>3</sup>Gedeon Richter Plc.*

**Background:** Bipolar I disorder is associated with morbidity, mortality, and disability. The Clinical Global Impression-Severity (CGI-S) scale measures the patient's global severity of illness. Unlike scales designed to measure specific symptom severity such as the Young Mania Rating Scale, the CGI-S can capture additional dimensions that contribute to disease severity such as comorbidity, patient distress, and functional impairment. Cariprazine is a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. Cariprazine was effective and well-tolerated in 3 double-blind, placebo-controlled trials in patients with bipolar mania (NCT00488618, NCT01058096, NCT01058668). Pooled data from these studies were used to evaluate the efficacy of cariprazine on overall severity of illness by measuring the percentage of patients that showed categorical improvement in CGI-S scores. **Methods:** All cariprazine doses were pooled for this analysis (2 studies: flexibly dosed 3-12 mg/d; 1 study: fixed/flexibly dosed 3-6 mg/d or 6-12 mg/d). The mean change in CGI-S score was the secondary efficacy measure in all 3 studies. This pooled analysis evaluated the proportion of patients who improved from a more severe CGI-S category at baseline to a less severe category at Week 3. The 3 different shift criteria analyzed were: 1) shifting from a baseline CGI-S score of  $\geq 4$  (moderately ill or worse) to  $\leq 2$  (borderline ill/normal) at Week 3; 2)  $\geq 5$  (markedly ill or worse) to  $\leq 2$  (borderline ill/normal); 3)  $\geq 6$  (severely ill or extremely ill) to  $\leq 3$  (mildly ill or better). For each of these categorical shifts, comparisons for cariprazine vs placebo were performed using a logistic regression model and odds ratios (OR) were determined. **Results:** At baseline, 97 patients (placebo, n=42; cariprazine, n=55) were severely or extremely ill, 637 patients (placebo, n=254; cariprazine, n=383) were at least markedly ill, and 1033 (placebo, n=428; cariprazine, n=605) were at least moderately ill. A significantly greater percentage of cariprazine vs placebo patients improved from moderately ill or worse at baseline to borderline ill/normal at Week 3 (32% vs 22%; OR=1.71; P<.001). Similarly, a greater percentage of cariprazine vs placebo patients shifted from markedly ill or worse to borderline ill/normal (markedly ill: 32% vs 18%; OR=2.10; P<.001). A greater proportion of cariprazine vs placebo patients shifted from severely or extremely ill to mildly ill or better (55% vs 36%; odds ratio [OR]=2.12; P=.09) but differences did not reach statistical significance, probably due to small sample size. **Conclusions:** In patients with manic or mixed bipolar I episodes, cariprazine was associated with clinically relevant improvements in global disease severity, as shown by the greater proportion of cariprazine vs placebo patients that shifted to less severe categories on the CGI-S after treatment.

### **Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the efficacy of cariprazine treatment on overall disease severity in patients with manic or mixed bipolar I episode.

- At the conclusion of this session, the participant should be able to compare the treatment effects of cariprazine in patients with different levels of global disease severity.

**Source of Funding:** Supported by Forest Laboratories, Inc, and Gedeon Richter Plc

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## **PSYCHOPHARMACOLOGY ALGORITHM FOR ACUTE MANIA**

*David Osser<sup>1</sup>, Othman Mohammad<sup>2</sup>*

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This is a new algorithm for the pharmacotherapy of acute mania developed by the Psychopharmacology Algorithm Project at the Harvard South Shore Program. The authors conducted a literature search in Pub Med and reviewed key studies, other algorithms and guidelines, and their references. Treatments were prioritized considering 3 main considerations: 1) effectiveness in treating the current episode, 2) preventing potential future relapses to depression, and 3) minimizing side effects over the short and long term. After accurate diagnosis, managing contributing medical causes including substance misuse, discontinuing antidepressants, and considering the patient's child-bearing potential, we propose different algorithms for mixed and non-mixed mania. Patients with mixed mania may be treated first with a second generation antipsychotic (SGA) of which the first-choice is quetiapine because of its greater efficacy for depressive symptoms and episodes in bipolar disorder. Valproate, and lithium or carbamazepine may then be added for unsatisfactory control of symptoms, in that order. For non-mixed mania, lithium is the first-line recommendation. An SGA can be added, and again quetiapine is favored, but if quetiapine is unacceptable, risperidone is the next choice. Olanzapine is not considered a first-line SGA due to its long term side effects, but it could be a second-line SGA. If the patient, whether mixed or non-mixed is still refractory to the above medications, then depending on what has already been tried, consider valproate, risperidone, olanzapine, haloperidol, and carbamazepine as first-tier, aripiprazole, ziprasidone, and asenapine as second-tier, and clozapine as third-tier because of its weaker evidence base and greater side effects. Electroconvulsive therapy may be considered at any point in the algorithm if there is a history of positive response or intolerance of medications.

### **Learning Objectives:**

- Attendees will be able to select medications for the treatment of acute mania from among the many choices with awareness of the evidence-base for efficacy and safety.
- Attendees will select medications for the treatment of acute mania with awareness of exceptions to usual practice due to comorbidity and other relevant circumstances.

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## **THE PSYCHOPHARMACOLOGY ALGORITHM PROJECT AT THE HARVARD SOUTH SHORE PROGRAM: 2014 UPDATE ON BIPOLAR DEPRESSION**

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**Background:** The psychopharmacology algorithm project at the Harvard South Shore Program published algorithms for bipolar depression in 1999 and 2010. Developments over the past 4 years suggest another update is needed. **Methods:** The 2010 algorithm and associated references were re-evaluated. A literature search was conducted on PubMed including review articles and recent studies to see what changes in the recommendations were justified. Exceptions to the main algorithm for special patient populations, such as patients with mixed states, ADHD, PTSD, substance use disorders, anxiety disorders, and women of childbearing potential and pregnant women, and those with common medical and psychiatric comorbidities were considered. **Results:** ECT is still a 1st line option for patients in need of urgent treatment. Lithium is still the first-line pharmacotherapy. There are now three choices for second line: lamotrigine and quetiapine from before, and lurasidone is added. If psychotic symptoms are present, lamotrigine is less favored. After sequential trials of these four treatments, the next node considers valproate which has a small evidence base, or an antidepressant (bupropion and SSRIs preferred). Olanzapine monotherapy and olanzapine/fluoxetine (FDA-approved) are still postponed due to metabolic side effects. In mixed and rapid cyler cases, avoid antidepressants. Combinations of the above options are considered in cases of partial response. **Conclusions:** This revision incorporates new treatments such as lurasidone and important new studies and organizes the evidence systematically.

### **Learning Objectives:**

- Readers will be able to select medications for bipolar depression with the best known effectiveness.
- Readers will be able to select medications for bipolar depression taking into account significant comorbidities and other patient features that change the standard approach.

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## **CORRELATION BETWEEN DIFFERENT LEVELS OF PLACEBO RESPONSE RATE AND CLINICAL TRIAL OUTCOME IN BIPOLAR DEPRESSION**

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*Massachusetts General Hospital, Harvard Medical School*

**Objective:** To investigate the relationship between specific levels of placebo response rates and the drug response rate and the relative risk of response to drug versus placebo in clinical trials of drug monotherapy for Bipolar Depression (BPD). **Methods:** PubMed was searched for studies published in the English language between January 1980 and January 2014 by using the search terms "placebo" and "bipolar". The search was supplemented by manual bibliographic review and examination of relevant review articles. The analysis included randomized, double-blind, placebo-controlled trials of pharmacotherapies used as monotherapy for BPD. **Results:** 17 monotherapy trials, representing a total of 25 active treatment versus placebo contrasts (4176 patients randomized to active treatment, and 2402 randomized to placebo) were found eligible for inclusion in our analysis. The response rates for subjects receiving active treatment or placebo were 55.1% (2302/4176) and 39.2% (942/2402) respectively, corresponding to a risk ratio for responding to active treatment over placebo of 1.29 (95% CI=1.21-1.37,  $p<0.001$ ). Similarly, the completion rate was 64.9% (2709/4176) and 62.4% (1498/2402) for active treatment and placebo respectively with a risk ratio for completing on active treatment over placebo of 0.995 (95% CI=0.95-1.04,  $p<0.822$ ). Finally, the rate of "switch" to abnormal elevated mood was 2.9% (102/3501) for subjects receiving active treatment and 3.9% (82/2060) for subjects receiving placebo, corresponding to a risk ratio of switch of 0.80 (95% CI=0.54-1.17,

$p < 0.0246$ ) for active treatment vs. placebo. Placebo response rates were found to be inversely correlated with the risk ratio of responding to drugs versus placebo ( $p = 0.002$ ). The pooled drug and placebo response rates for studies with a placebo response rate  $\leq 30\%$  were 50.5% versus 26.6%, while corresponding values from studies with a placebo response rate  $> 30\%$  were 55.5% versus 40.3%. Conclusions: These results suggest that the relative efficacy of the active drug compared to placebo in clinical trials for BPD is highly heterogeneous across studies with different placebo response rates, with a worse performance in showing a superiority of the drug versus placebo for studies with placebo response rates  $> 30\%$ . It is important to maintain placebo response rates below this critical threshold, since this is one of the most challenging obstacles for new treatment development in BPD. References: Papakostas GI, Fava M: Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol* 2009; 19:34-40 Iovieno N, Papakostas GI: Correlation between different levels of placebo response rate and clinical trial outcome in major depressive disorder: A meta-analysis. *J Clin Psychiatry* 2012; 73:1300-1306.

### **Learning Objectives:**

- A high placebo response rate in clinical trials for BPD is one of the most challenging obstacles for new treatment development.
- It is important to maintain placebo response rates below the threshold of 30%.

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### **RESILIENCE IN HIGH-RISK INFANTS AND TODDLERS OF MOTHERS WITH BIPOLAR DISORDER: A LONGITUDINAL INVESTIGATION**

*Diana I. Simeonova, Theresa Nguyen, Kerry Ressler, W. Edward Craighead  
Emory University School of Medicine*

**Aims:** There is growing evidence that approximately 50% of high-risk offspring of parents with bipolar disorder (OBD) develop moderate to severe forms of psychopathology during childhood and adolescence, including bipolar spectrum disorders. Despite exposure to multiple risk factors, however, the remaining 50% of OBD follow normative and resilient developmental trajectories and do not experience psychopathology. Currently, very limited knowledge exists on resilience in this population and mechanisms contributing to adaptive development remain unknown. The present study, an investigation of high-risk infants and toddlers and their mothers with BD from birth until two years of age, aims to address this gap in the literature. The study findings have the potential to: 1) serve as a translational platform for prevention and early intervention initiatives, 2) aid to delineate mechanisms contributing to adaptive trajectories, and 3) guide the development of targeted early interventions for an appropriate subgroup of children at the youngest possible age. **Methods:** A repeated-measures design was used to assess mothers and infants during a pregnancy screening visit and at 5-7 days, 3, 6, 12, 18, and 24 months postpartum. Clinician-rated, maternal, and infant measures were completed at each visit. The clinician-rated measures include: SCID-I, SCID-I Mood Module, Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, Mania Rating Scale, and Global Assessment of Functioning Scale. The maternal measures include: Postpartum Social Support Questionnaire, Social Support Questionnaire, Social Adjustment Scale, Dyadic Adjustment Scale, Parenting Sense of Competence Scale, Beck Depression Inventory I, and State-Trait Anxiety Inventory. The infant measures include: Brazelton Neonatal Behavioral Assessment Scale, Infant Behavior Questionnaire-Revised, Early Child Behavior Questionnaire, Ages and Stages Questionnaire:

Social-Emotional, and Infant-Toddler Social and Emotional Assessment. In addition, mother-infant interactions focused on emotion regulation and other domains of interest were conducted. Face-to-Face Still-Face paradigm, free play, and feeding were recorded and pre-and post-interaction saliva was collected to assay for oxytocin. Results: 14 women with BD (mean age=32.5; SD=3.9; range=25-39; BD I=8; BD II=6) were enrolled in the study during pregnancy. The recruitment and data collection are ongoing. To date, 10 infants were born into the study (male=6; female=4) and the following study visits were completed: screening visit (n=14), 5 days postpartum (n=10), 3 months postpartum (n=8), 6 months postpartum (n=6), 12 months postpartum (n=4). Conclusions: This longitudinal investigation is the first study to enroll mothers with BD during pregnancy and to follow a cohort of OBD during the earliest stages of development. The emerging data has the potential to: 1) facilitate answers to research questions focused on the trajectory of social-emotional development, mother-infant interaction, and resilience and risk factors in infants and toddlers of mothers with BD, and 2) inform the development of novel prevention and early intervention approaches based on resilience models.

### **Learning Objectives:**

- To inform researchers and clinicians about the rationale and importance of investigating resilience in high-risk offspring of parents with bipolar disorder.
- To inform researchers and clinicians about an ongoing longitudinal investigation of infants and toddlers of mothers with bipolar disorder and the potential of this research to contribute to the development of novel prevention and early intervention approaches.

### **Literature References:**

- Cicchetti, D. (2010). Resilience under conditions of extreme stress: a multilevel perspective. *World Psychiatry*, 9, 145-154.
- Carter, A., Briggs-Gowan, M., & Davis, N. (2004). Assessment of young children's social-emotional development and psychopathology: Recent advances and recommendations for practice. *Journal of Child Psychology and Psychiatry*, 45, 109-134.

**Source of Funding:** K23 Mentored Patient-Oriented Research Career Development Award from NIMH

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## **A DIMENSIONAL ASSESSMENT OF ANXIETY AND TIC SEVERITY IN TOURETTE'S DISORDER**

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Tourette's Disorder (TD) is a developmental neuropsychiatric illness characterized by vocal and multiple motor tics for more than one year with onset before age 18 years. The aim of this study is to explore the relationship between anxiety and tic severity in a clinically referred, well-characterized sample of children and adolescents with Tourette's Disorder (TD). Method: TD subjects were referred to a tics and Tourette's research clinic between 2002 and 2011 for inclusion in tic disorder studies; none were referred for anxiety. Healthy controls (HC) were evaluated between 2005 and 2010 at a pediatric mood and anxiety disorders clinic; all enrolled HC subjects did not meet criteria for any major current or past DSM-IV-TR diagnoses and had never received psychotropic medication. The associations between baseline Yale Global Tic

Severity Scale (YGTSS) and Multidimensional Anxiety Scale for Children (MASC) scores were examined using bivariate correlations and multiple linear regression. Results: The sample consisted of 109 individuals, including 72 subjects, ages 6.5-17.2 years ( $M = 11.5 \pm 2.6$ ), who met DSM-IV-TR diagnostic criteria for TD and 37 healthy controls ages 11.3-19.5 years ( $M = 15.5 \pm 2.1$ ). Of the TD subjects, forty-one (56.9%) met criteria for Attention Deficit Hyperactivity Disorder (ADHD); 26 (36.1%) met criteria for Obsessive Compulsive Disorder (OCD); and 22 (30.6%) met criteria for at least one non-OCD anxiety disorder. MASC Total Anxiety T-score distribution functions were significantly higher in TD than HC. YGTSS vocal tic, total tic, tic-related impairment, and global severity scores were significantly positively correlated with MASC Total Anxiety scores. YGTSS tic-related impairment and global severity scores were significantly positively correlated with MASC Social Anxiety subscale scores. YGTSS total tic scores were significantly different in the top and bottom 25% of the sample as grouped by MASC Total Anxiety T-scores. MASC Total Anxiety scores were more robust predictors of YGTSS tic-related impairment and global severity scores than comorbid diagnoses of non-OCD anxiety disorder, OCD, or ADHD. Conclusion: Our findings, while preliminary, provide support for a significant relationship between anxiety and tic severity within a clinically referred, well-characterized sample of youth with TD. Findings suggest that higher levels of anxiety severity may predict higher tic severity. It is possible that anxiety may predict greater overall illness severity in children and adolescents with TD. If these results are replicated in additional samples, a dimensional measure of anxiety may be an important addition to evaluation of tic severity and treatment planning.

### **Learning Objectives:**

- To explore the relationship between anxiety and tic severity in a clinically referred, well-characterized sample of children and adolescents with Tourette's Disorder (TD).
- To explore the merits of evaluation of anxiety symptomatology using dimensional measures in TD subjects.

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## **COMPUTERIZED ADAPTIVE DIAGNOSIS AND TESTING IN PSYCHIATRIC OUTPATIENTS SEEKING CARE AT A LARGE, FREE-STANDING PSYCHIATRIC HOSPITAL**

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The Computerized Adaptive Test-Mental Health or CAT-MH, is a collection of three adaptive tests for depression, anxiety, and mania, and a diagnostic screening test for major depressive disorder (CAD-MDD) developed as part of an ongoing program of research funded by the National Institute of Mental Health (1-4). The CAD-MDD produces a remarkably accurate screening diagnosis of depression (5). The three computerized adaptive tests produce continuous severity scores that can be used for both assessment and monitoring. The paradigm shift between traditional screening and assessment tools and those associated with these tests is that they begin with a large "bank" of items (1008 psychiatric symptom items) and adaptively administer a small and statistically optimal subset of the items (on average 12 items for each of the three CATs and 4 items for the CAD-MDD) fixing the level of precision. Each of the CATs maintains a correlation of close to  $r=0.95$  with the entire bank of items for each test (389 depression items,



431 anxiety items, 88 mania items). This study sought to validate the utility of CAD-MDD and the CAT-MH suite of tests (CAT-DI, CAT-ANX, and CAT-MANIA) for assessing cross-cutting psychiatric symptom severity in a community sample of adult psychiatric outpatients. 145 individuals, aged 18-70 years, with a range of psychiatric diagnoses seeking access to care at Pine Rest Christian Mental Health Services, a large, free-standing psychiatric treatment facility located in Grand Rapids Michigan, and healthy controls, were evaluated using the above measures in addition to gold-standard diagnostic and severity scales including the SCID for DSMIV-TR (6), CES-D (7), PHQ-9 (8), HAM-D25 (9) and GAF (10). Patient satisfaction with computerized testing was also measured. Results from this cross-sectional, prospective study showed the overall sensitivity and specificity for MDD was 0.96 and 0.64, respectively. Restricting the sample to patients with MDD and healthy controls yielded sensitivity of 0.96 and specificity of 1.0. High correlations (0.73 to 0.90) were found for the CAT depression (0.79 to 0.90) and anxiety (0.73 to 0.81) assessments with the standard depression scales. Each CAT significantly predicted the corresponding SCID diagnosis. Subjects found the CAT-MH suite of tests easy to use, averaging 51.7 items and 9.4 minutes to complete it. This methodology has the potential to substantially improve the assessment of patients for whom access to expert clinicians is limited and thereby enable more precise selection of personalized treatment. In the future, this technology could be used to facilitate population-level assessment of mental health disorders via cloud computing environments using secure servers and electronic health record integration.

#### **References:**

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- Gibbons RD, et al. Am J Psychiatry 2013; (Aug 9, Epub ahead of print).

#### **Learning Objectives:**

- Discuss the difference between traditional fixed length psychiatric assessments and adaptively administered tests.
- Discuss the results from a cross sectional, prospective study to assess psychiatric symptoms in a real world clinical setting.

**Source of Funding:** This work was supported by grants from the Pine Rest Foundation (Halstead, Achtyes), and the National Institute of Mental Health MH66302 (Gibbons), and in-kind support of computer software from Michigan State University (Achtyes).

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## **A DIMENSIONAL RATING SYSTEM FOR PSYCHIATRIC DISORDERS IN PSYCHIATRIC OUTPATIENTS**

*Mark Zimmerman*

*Rhode Island Hospital*

**Objective:** A common criticism of contemporary psychiatric nosologies such as DSM-IV is that they are based on a categorical approach towards classification rather than a dimensional representation of levels of psychopathology. For personality disorders multiple lines of research clearly favors a dimensional model over categorical classification. Comparable literature comparing dimensional and categorical classification models across a range of Axis I disorders is lacking. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment

and Services (MIDAS) project we describe the development of a dimensional rating system for Axis I disorders. Methods: One thousand six hundred psychiatric outpatients were evaluated with semi-structured diagnostic interviews for DSM-IV Axis I and Axis II disorders and measures of psychosocial morbidity. A Standardized Clinical Outcome Rating (SCOR), a 7-point dimensional rating, was made for 18 Axis I disorders. Results: The dimensional ratings were made with high reliability. The total SCOR, summed across all 18 dimensions, was significantly correlated with each measure of psychosocial morbidity. The mean of the correlations was higher with the total SCOR than the number of Axis I disorders (.36 vs. .31). After controlling for the number of Axis I disorders, each of the partial correlations between the dimensional rating and the measures of psychosocial morbidity was significant (mean partial  $r = .21$ ). However, when the dimensional score was controlled, then none of the partial correlations between the categorical index and measures of psychosocial morbidity were significant (mean partial  $r = .03$ ). Discussion: Dimensional ratings of Axis I disorders can be made reliably and validly. The SCORs are brief standardized outcome ratings that can be incorporated into routine clinical practice without adding undue burden to the treating clinician. These ratings could make it more feasible to conduct effectiveness studies in clinical practice, and to extend measurement-based care paradigms to clinical ratings.

### **Learning Objectives:**

- At the conclusion of this presentation the participant will become familiar with a dimensional rating system for Axis I disorders that can be incorporated into clinical practice.
- At the conclusion of this presentation the participant will become familiar with data demonstrating that a dimensional ratings of disorders are more highly correlated with psychosocial morbidity than categorical diagnostic determinations.

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### **A CLINICALLY USEFUL SELF-REPORT MEASURE OF THE DSM-5 ANXIOUS SPECIFIER OF MAJOR DEPRESSIVE DISORDER**

*Mark Zimmerman*

*Rhode Island Hospital*

Objective: To acknowledge the clinical significance of anxiety in depressed patients, DSM-5 included criteria for an anxious features specifier for major depressive disorder. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project we describe a modification of a self-administered depression scale to include a subscale assessing the DSM-5 anxious features specifier of major depressive disorder. Methods: Nearly 800 psychiatric outpatients with major depressive disorder completed the Clinically Useful Depression Outcome Scale (CUDOS) supplemented with questions for the DSM-5 anxious features specifier (CUDOS-A). The patients were rated on clinician severity indices of depression, anxiety and anger. Discriminant and convergent validity was examined in a subset of patients who completed other self-report symptom severity scales, and test-retest reliability was examined in a subset who completed the CUDOS-A twice. We compared patients who did and did not meet the DSM-5 anxious features specifier on indices of psychosocial functioning and quality of life. Results: The CUDOS-A subscale had high internal consistency and test-retest reliability, and was more highly correlated with other self-report measures of anxiety than with measures of depression, substance use problems, eating disorders, and anger. The CUDOS-A

was more highly correlated with clinician severity ratings of anxiety than depression and anger, and CUDOS-A scores were significantly higher in depressed outpatients with a current anxiety disorder than depressed patients without a comorbid anxiety disorder. Finally, depressed patients who met the DSM-5 anxious features specifier reported poorer psychosocial functioning and quality of life than depressed patients who did not meet the anxiety specifier. Conclusion: The results of this large validation study of the CUDOS-A shows that it is a reliable and valid measure of the DSM-5 anxious features specifier for major depressive disorder.

### **Learning Objectives:**

- At the conclusion of this presentation the participant will become familiar with the reliability and validity of a self-report depression scale that has been modified to assess the DSM-5 anxious features specifier.
- At the conclusion of this presentation the participant will become familiar with the significance of assessing anxiety in depressed patients.

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### **REDUCTION OF PLACEBO RESPONSE IN DEPRESSION TRIALS VIA INDEPENDENT REMOTE (SAFER) PATIENT INTERVIEWS**

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Objective: Systematic approaches are required to increase the quality and precision of clinical trials for major depressive disorder (MDD). The development of new treatments for MDD and treatment resistant depression (TRD) is hindered by high placebo response rates that impair ability to identify signals of efficacy from potentially promising new therapies. Background: In order to increase the precision in making the correct diagnosis of MDD and of treatment resistance, our group has created and implemented two clinical trial tools. The SAFER Interview and the Antidepressant Treatment Response Questionnaire (ATRQ) are designed to provide clinical researchers with user friendly tools to enrich the qualitative assessment of MDD and treatment resistance. This reliable assessment of the patient's diagnosis and severity is made in a way that reflects the illness in a real-world setting. Methodology: A retrospective review of SAFER and ATRQ interviews conducted in five clinical drug trials in TRD was performed. In each trial, all subjects had passed screening procedures at the site and were considered to be eligible for the trial. A structured severity interview was performed in addition to the SAFER and ATRQ. The SAFER interview was performed remotely by clinicians from Massachusetts General Hospital, who called the patient directly. The interview typically took 45 minutes. Results: Across five independent trials of TRD, 2308 remote SAFER interviews were performed. Of the 2308 interviews, 1,562 patients were deemed eligible for continued screening. Of the remaining patients, 97 (4%) did not meet severity criteria, 39 (2%) did not meet only SAFER criteria, 151 (7%) did not meet ATRQ criteria for treatment resistance, and 86 (4%) did not meet criteria on more than one component of the SAFER Interview. A total of 373 (16%) of the patients were deemed ineligible upon completion of the interview. In all of the studies, placebo response rates were within a range of 18-28%, below the 30-37% average in studies of treatments approved for TRD (olanzapine-fluoxetine combination, quetiapine and aripiprazole).

Conclusion: A substantial proportion of potential participants in drug trials of TRD are excluded based on the rigorous application of these tools. If SAFER interviews were not applied, many inappropriate patients would likely have been included impairing assay sensitivity and potentially resulting in a failed trial. These methods enhance the quality of clinical trials and increase the likelihood of positive trials for efficacious compounds, based on low placebo response rates when the appropriate patients are enrolled. References: Chandler GM, Iosifescu DV, Pollack MH, Targum SD, and Fava M. Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). *CNS Neurosci Ther* 2010. 16(5):322-5. Targum SD, Pollack MH, Fava M. Redefining affective disorders: relevance for drug development. *CNS Neurosci Ther*. 2008; 14: 2–9.

### **Learning Objectives:**

- Patient Selection
- Study Methodology

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### **A COMPARISON OF CROSS-CULTURAL REGIONAL NORMS FOR THE MATRICS CONSENSUS COGNITIVE BATTERY (MCCB)**

*Ioan Stroescu<sup>1</sup>, Vicki G. Davis<sup>1</sup>, Alexandra S. Atkins<sup>1</sup>, Richard S. E. Keefe<sup>2</sup>*

*<sup>1</sup>NeuroCog Trials, Inc., <sup>2</sup>NeuroCog Trials, Duke University*

Introduction (Aims): The rise in international clinical trials that include cognitive, behavioral, and functional outcomes has increased interest in the psychometric characteristics of performance-based measures in different languages and cultures. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative has facilitated the development and application of guidelines for pharmaceutical trials involving neurocognitive outcomes in schizophrenia. The MATRICS Consensus Cognitive Battery (MCCB) is now widely used in international trials examining potential improvement in cognition in patients with schizophrenia. Several individual tests from the MCCB have been used with various international populations, however the potential benefit of using regional versus U.S. based normative corrections for MCCB composite scores is currently uncertain. The impact of these corrections on signal detection is also of interest. To address these questions, we examined differences between MCCB composite scores calculated using standard U.S. norms and those calculated using regional normative data sets. Methods: MCCB data composite scores were generated from regional normative adjustments (in several different languages) and compared to scores generated from U.S. norms. Baseline MCCB composite T-scores with normative adjustments from local, language-specific cohorts in India (Hindi: N=60 & N=28), China (Simplified Chinese: N=247), Russia (N=225), and Central and South America [CSA] (Colombia, Mexico, Chile, & Argentina: N=175) were examined. The difference in change score distributions was assessed when possible, based on data availability. Results: Results generated from regional normative adjustments differ with regard to their comparability to U.S. normative adjustments. Normative corrections based on regional data collected in China yield a one standard deviation (SD) increase in baseline MCCB composite T-scores relative to U.S. norms, while application of Russian norms had negligible effects. Results from CSA and India show a greater than two standard deviation (SD) increase in baseline T-scores relative to the application of US norms. The mean (+/- SD) changes in composite T-scores and effect sizes (Cohen's d) from baseline to week 24 were 7.3 (+/- 7.57; d = 1.0) using Hindi-based norms and 8.8 (+/- 8.60;

d = 1.0) using US norms in one sample on active treatment. Conclusions: Cross-cultural validity of measures is important to the success of international clinical trials with neurocognitive and behavioral endpoints. For measures such as the MCCB, which rely on normative correction, improving the applicability of norms to the population of interest has the potential reduce noise due to cultural differences alone. Our results suggest the choice of normative data sets may have a considerable impact on the baseline characterization and selection of subjects (depending on the region and language). The impact on change scores is less certain. Additional analyses on large data sets are necessary to determine the impact of local norms within each language and culture, and to assess the extent to which the use of regional norms may facilitate signal detection.

### **Learning Objectives:**

- Gain an appreciation for the importance and use of appropriate normative data in clinical trials.
- Examine differences between local versus standard normative corrections on MCCB composite scores.

**Source of Funding:** Funding for this study was provided by NeuroCog Trials, Inc. I Stroescu, V Davis and AS Atkins are full-time employees of NeuroCog Trials, Inc. RSE Keefe is founder, CEO, and a shareholder in NeuroCog Trials, Inc.

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### **MAGNITUDE OF CHANGE WITH ANTIDEPRESSANTS AND PLACEBO IN ANTIDEPRESSANT CLINICAL TRIALS USING STRUCTURED, TAPED AND APPRAISED RATER INTERVIEWS COMPARED TO TRADITIONAL SEMI-STRUCTURED INTERVIEWS**

*Arif Khan<sup>1</sup>, James Faucett<sup>1</sup>, Walter Brown<sup>2</sup>*

*<sup>1</sup>Northwest Clinical Research Center, <sup>2</sup>Brown University*

**Background:** It has been suggested that variability and unpredictability of response to antidepressants and placebo in antidepressant clinical trials is due in part to inconsistent and heterogeneous rating interviews by clinical trial raters. As a result of this suggestion investigators have proposed methods such as the Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA) with audio taping and outside appraisal of the interviews throughout the trials using Rater Applied Performance Scale (RAPS) criteria (1,2). These proposals were based in part on post-hoc studies of audio taped depression interviews and have led to the use of SIGMA interviews with taping and outside RAPS appraisal in several pivotal antidepressant clinical trials in the past five years. However, there is limited evidence that these methods actually increase antidepressant-placebo differences. **Methods:** We reviewed data from patients that were screened (N=243) and randomized (N=148) in four clinical trials of approved antidepressants: two of which used SIGMA interviews and two of which used traditional semi-structured Montgomery-Asberg Depression Rating Scale (MADRS) interviews. We first assessed similarity of the protocols of the trials using the respective interview methods. Primary analyses evaluated antidepressant-placebo differences in the trials using taped SIGMA interviews with outside appraisal as well as in the trials using traditional semi-structured MADRS interviews. **Results:** In trials using taped SIGMA interviews with outside appraisal there were no significant differences in response between patients assigned to antidepressants versus those assigned to placebo at any time during the eight-week trials. In trials using

traditional semi-structured MADRS interviews patients assigned to antidepressants had a significantly greater response than those assigned to placebo,  $F(df=5)=11.1$ ,  $p<0.001$ . In fact, a post hoc series of independent samples t tests found that the difference between treatment groups was significant from the second week through the eighth and final week of the trials.

Conclusions: These results are unexpected and contrary to both expectations and the rationale that prompted the design and introduction of SIGMA interview techniques with audio taping and outside RAPS appraisal. New interview methods, no matter how apparently self-evident in their value, need prospective testing prior to implementation.

### **Learning Objectives:**

- To evaluate structured depression interviews with taping and outside appraisal that are being used in antidepressant clinical trials increase the antidepressant-placebo differences as intended.
- To evaluate the possibility that depression rating style is a factor that may influence antidepressant clinical trial outcome.

**Source of Funding:** There is no external funding source for this presentation. All of the authors were salaried by their institutions with no specific funds being set aside for this project. We are advocating traditional psychiatric interviews which has no proprietary value.

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## **THE IMPACT OF IMPLEMENTING A NATIONAL RESEARCH SUBJECT DATABASE TO PREVENT DUAL ENROLLMENT IN EARLY AND LATE PHASE CENTRAL NERVOUS SYSTEM TRIALS**

*Mitchell Efros, Kerri Weingard*

*Accumed Research Associates & Verified Clinical Trials*

Objective To develop a system to prevent dual enrollment in clinical trials. Enrollment in CNS clinical trials can present unique and considerable challenges to research sites, pharmaceutical companies and CRO's. The research subject's failure to admit to simultaneous participation in more than one clinical trial and jumping from one trial to another without allowing sufficient time to lapse between treatments compromise both the health of the subjects, data quality and the outcome of the trial. The issue of dual enrollment in clinical trials is widespread, especially in the CNS clinical trials. When a research subject combines multiple investigational products or alternatively does not actually take the study product and provides false data, this leads to altered efficacy rates, placebo rates, and potential for increased adverse events. Dual enrollment is a serious problem that can be costly to the research site, pharmaceutical company and most importantly, harmful to patients. Method Using a proprietary IDmetric HIPAA compliant de-identified research subject clinical trials registry database system, Verified Clinical Trials has successfully performed 184,590 verifications and dual screening alerts over the past 2 years in North America. Both early phase and late phase trials were incorporated in to the Verified Clinical Trials system. Following informed consent, several different types of checkpoints and alerts are run with each verification just prior to screening for the clinical trial. Results A significant amount of subjects attempting of screen in clinical trials were found to be problematic. 4% of the subjects attempted dual enrollment across all phases of clinical research and all disease states. A much higher incidence was seen in early phase trials where stipends were higher and in certain disease states such as healthy volunteers, CNS, pain and other

subjective conditions. Attempted dual enrollment was thwarted with the database registry. Furthermore, overall cost were reduced by stopping the attempted dual enrollment prior to screening and preventing costly screenings. The system detected 7% attempted enrollment during their lockout period across all phases of clinical research with similar statistics across early and late phase trials. 5% attempted to screen while actively screening at another clinical trial center. By tracking the dual screening activity Verified Clinical Trials was able to alert those CNS research centers, allowing them to be pro-active with qualified alternates to meet their enrollment and dosing numbers. 97% of research subjects accepted the verification system at screening and the added security and safety measures of a clinical trials research subject database system had very little, if no impact on successful screening and enrollment in CNS clinical trials. Conclusion The system has achieved recognition and uptake by individual sites, pharmaceutical clinical trial sponsors and CROs. The system has been IRB reviewed and applauded as it improves patient safety. Verified Clinical Trials is a mature and robust research subject database registry system replete with data on dual enrollment in clinical trials in North America. With time, increased use of a research subject clinical trials database system will result in better quality research subject screenings and better quality data with improved safety. This is especially useful in CNS trials where dual enrollment is prevalent.

#### **Learning Objectives:**

- To establish the presence and state the frequency of dual enrollment in CNS clinical trials with mature data beyond a pilot phase while providing details on the impact on patient safety & data quality in early and late phase clinical trials research.
- To elucidate an existing solution to the problem of dual enrollment and discuss the issues that surround creation of a national clinical trials database registry that has significant data.

**Source of Funding:** Self-funded by Mitchell Efros MD FACS

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#### **EARLY LIFE STRESS AS A RISK FACTOR FOR SUBSTANCE USE DISORDERS: CLINICAL AND NEUROBIOLOGICAL SUBSTRATES**

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*Rosalind Franklin University of Medicine and Science*

Early Life Stress (ELS) can profoundly influence an individual's genotype and phenotype. Effects of ELS can manifest in the short-term as well as later in life and even in subsequent generations. The foregoing ELS activate corticotrophin releasing factor (CRF). Mounting evidence indicates that CRF influences drug seeking and drug addiction. However, the effects of endogenous elevated levels of CRF on drug addiction are unknown. We investigated whether conditionally CRF over-expression (CRF-OE) in the forebrain increases the vulnerability to opioid addiction. We demonstrate that in CRF-OE mice show increased sensitization and withdrawal symptoms after morphine administration compared to wild-type mice. On the basis of the foregoing hypothesis; while we translate this from bench to bedside, we speculate that patients with a history of ELS are at high risk to develop opioid use disorder and other substance use disorders (SUD). One of the reasons to develop SUDs may be due to increased levels of CRF that increases morphine-induced sensitization and increased risk and severity of withdrawal

symptoms. This may shed light on the neuropharmacological basis of SUDs and other addictive behaviors.

### **Learning Objectives:**

- To understand the role of over-expressed CRF in Early Life Stress (ELS) and Substance Use Disorders (SUD).
- To explain the mechanism of ELS as a risk factor for SUD.

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### **PANIC DISORDER: THEORETICAL OVERLAP WITH NARCOLEPSY**

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Background: Excessive daytime drowsiness (EDS), sleep-related hallucinations, sleep paralysis, and cataplexy are the symptomatic tetrad of narcolepsy. Recent studies have found that anxiety disorders, particularly panic disorder, are also associated with insomnia, EDS, as well as cataplexy. Taken together, these findings suggest a symptomatic overlap and possible shared biological diathesis between some subtypes of panic disorder and narcolepsy with cataplexy. Although approximately 65% of panic disorder patients report a lifetime prevalence of sleep panic attacks, none of these earlier studies carefully differentiated wake versus sleep panic attacks when examining the proportion of panic disorder patients reporting classic symptoms of narcolepsy. Methods: This preliminary study examined the rates of hypersomnia, hypnogogic/hypnopompic hallucinations and cataplexy in well-characterized normal healthy controls (n=10), panic disorder patients (wake panic alone; n=6), subjects with recurrent isolated sleep paralysis (ISP; n=13) and patients with co-morbid panic disorder plus isolated sleep paralysis (n=8). None of the patients had ever been evaluated, treated, or even suspected of having narcolepsy at the time of their referral to our anxiety clinic. Results: Despite our small samples, there was a highly significant association between any type of panic (wake and/or sleep panic attacks) plus sleep paralysis and self-reported hypersomnia (Chi-square, 28.7, df=4, p<.000) and hypnopompic hallucinations (Chi-square, 16.2, df=4, p<.003), with a similar trend for hypnogogic hallucinations (p=.097). While only 13.5% of the total sample reported both lifetime hypnopompic and hypnogogic hallucinations, four of the five (80%) individuals who reported both types were in the group of anxiety disordered patients with a history of panic attacks plus recurrent isolated sleep paralysis. Only two patients met criteria for cataplexy; however, both of these individuals reported wake panic attacks plus either sleep panic or recurrent isolated sleep paralysis. Finally, a patient referred for treatment of panic disorder (who had an initial positive but later refractory response to an SSRI) was positive for HLA-DQB1\*06:02, which is strongly associated with narcolepsy. This same patient had a low CSF hypocretin-A level (58.8 pg/mL), which is below the 110 pg/mL cutoff level required by DSM-5 to meet diagnostic criteria for narcolepsy without cataplexy but with hypocretin deficiency. Conclusion: Our findings reinforce earlier observations suggesting the need to investigate the neurobiological relationship between anxiety disorders and narcolepsy. Our findings further suggest that patients with any type of panic attacks (i.e. wake or sleep) plus recurrent isolated



sleep paralysis may be a particularly worthwhile group to investigate for identifying such a relationship. From a practical perspective, our findings suggest that clinicians should consider more formal diagnostic testing such as PSG, MSLT, HLA-typing or, possibly, even CSF hypocretin levels in patients with anxiety plus cataplexy or in patients presenting with wake and/or sleep panic attacks plus recurrent isolated sleep paralysis.

### **Learning Objectives:**

- To learn how to identify possible narcolepsy in patients presenting with panic disorder.
- To identify indications for additional sleep diagnostic studies and CSF laboratory testing in patients with co-morbid panic attacks and recurrent isolated sleep paralysis.

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### **A FIVE YEAR OBSERVATIONAL STUDY OF PATIENTS WITH TREATMENT RESISTANT DEPRESSION TREATED WITH VNS THERAPY® OR TREATMENT AS USUAL: COMPARATIVE RESPONSE/REMISSION RATES, DURATION OF RESPONSE, AND QUALITY OF LIFE**

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**BACKGROUND:** Patients with treatment-resistant depression (TRD) have comorbid illnesses, take multiple medications, and require lifetime treatment. While recommendations have been suggested for treatment, no studies have looked at the long term effects of treatment interactions for these patients. VNS Therapy® (VNS) has been shown to be safe and effective to treat TRD (1,2) and is FDA approved for adjunctive long-term treatment of chronic or recurrent depression for patients over the age of 18 who are experiencing a major depressive episode (MDE) that have not had an adequate response to 4 or more adequate antidepressant treatments. **OBJECTIVES:** A prospective, open label registry to follow the clinical course and outcome for patients with TRD treated with and without adjunctive VNS Therapy. Response/remission rates, duration of response, and quality of life data are to be presented. **METHODS:** A Registry was conducted as a long-term, prospective, observational, effectiveness study in 61 US centers. Adults with chronic depression at least two years in duration or with a recurrent depression that included at least 3 or more MDEs were enrolled from 2006 to 2010. Patients must have experienced at least four adequate, yet unsuccessful, antidepressant treatments and have chosen at screening to be implanted with VNS Therapy or receive treatment as usual (TAU). Physician and patient assessments were completed over the course of 5 years. Patient evaluations included the MADRS, CGI-I, and Q-Les-Q scale and will be reported. **RESULTS:** The VNS Therapy arm and TAU arm consisted of 494 and 301 patients, respectively. Females were 349 (70.6%) in the VNS arm and 210 (69.8%) in TAU. Average age at baseline was 49.3 years. Age at initial depression diagnosis was 29.1 years. Average number of failed treatments was 7.9. **MADRS:** Patients in the VNS Therapy arm were more likely to experience remission than patients in the TAU arm over a 5-year period (43.1% for VNS vs. 22.8% for TAU,  $P < 0.0001$ ). Median remission duration was longer for the VNS Therapy than the TAU based on MADRS scores (40 months for VNS vs. 19 months for TAU,  $P < 0.0065$ ). **CGI:** Patients in the VNS Therapy arm showed greater response than patients in the TAU arm over the 5-year period (75.7% for VNS vs. 47.1% for TAU,  $P < 0.0001$ ). The VNS Therapy arm showed consistently better quality of life (Q-Les-Q) over the 5-year period than TAU ( $p < 0.0001$ ). The score difference was 3.53, 4.69, 4.86, 4.86, and 5.63 points in favor of VNS Therapy at 12, 24, 36, 48, and 60 months, respectively. **CONCLUSIONS:**

Adding VNS Therapy results in superior outcomes over a 5-year period compared to TAU for patients with a chronic or severe course of TRD. REFERENCES: 1 Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL, et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: Acute and chronic effects. *Brain stimulation*. 2012. 2 Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biological psychiatry*. 2005;58(5):355-63.

### **Learning Objectives:**

Rates of remission for depressed patients with treatment resistant depression.

Duration of remission for depressed patients with treatment resistant depression.

**Source of Funding:** Cyberonics, Inc.

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### **PRENATAL STRESS INFLUENCES THE PROPER FUNCTIONING OF THE PRIMARY MICROGLIAL CELLS AND LEADS TO BEHAVIORAL CHANGES IN ADULT OFFSPRING - A LINK TO DEPRESSION**

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**Objectives** Despite many years of research the pathomechanism of depressive disorder still remains unknown. It requires further investigation and points to the usefulness of animal models of depression, including prenatal stress procedure [Morley-Fletcher et al., 2003]. Recent data suggest that stress occurring during pregnancy leads to disturbances in neurodevelopment by affecting neuron-glia interactions in the offspring. The key role of changes in the inflammatory status and neurotrophic factors e.g. insulin like growth factor 1 (IGF-1) has been postulated [Madhusudan et al., 2013]. The target of present study was to verify whether prenatal stress procedure results in behavioral changes in adult offspring. In the set of experiments aimed to study the potential cause of these disturbances, the primary microglia cells obtained from young prenatally stressed offspring were tested. **Method** Pregnant Sprague-Dawley rats were subjected daily to three (at 9.00, 12.00, 17.00) stress sessions from 14th day of pregnancy until delivery. Control pregnant females were left undisturbed in their homecages. At the age of 3-months behavioral verification was conducted (sucrose preference, elevated plus maze and forced swim tests). In the second part of study the primary microglial cell cultures were prepared from the cortices of 1-2 days old Sprague-Dawley control and prenatally stressed rats. Cells were maintained for 8 days in DMEM supplemented with 10% FBS and 1% antibiotics. Next, microglial cells were plated onto plates and after 48 h of cell culture stabilization the changes in viability (LDH test), proliferation (MTT method) and morphology [light or immunofluorescence (IBA-1) microscopy] were evaluated. The expression of IGF-1 and pro-inflammatory cytokines was quantified by qRT-PCR method. **Result** Prenatal stress procedure induces depression-like disturbances in adult rats. An increase in immobility, decrease in swimming (Porsolt test), potentiation of anxiety- and anhedonic-like behavior were observed. Furthermore, present data indicate that primary microglia cells obtained from young prenatally stressed animals showed altered morphology, viability and proliferation. Additionally, decreased expression of IGF-1 was

accompanied by enhanced expression of pro-inflammatory cytokines: IL-1b, IL-18 TNF-a and IL-6. Conclusion Our results suggest that exposure to prenatal stress may have an important influence on the primary microglial cells functioning. These disturbances may increase the risk of onset of pathological processes involved in the development of depressive disorder.

### Learning Objectives:

- Morley-Fletcher S., Darnaudery M., Koehl M., Casolini P., Van Reeth O., Maccari S.: Prenatal stress in rats predicts immobility behavior in the forced swim test. Effects of chronic treatment of tianeptine. *Brain Res.*, 2003, 989, 246-51.
- Madhusudan A., Vogel P., Knesel I.: Impact of prenatal immune disturbances on brain development. *J. Neuroimmune. Pharmacol.*, 2013, 8, 79-86.

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## THE EFFICACY OF VILAZODONE IN ACHIEVING REMISSION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: POST HOC ANALYSES OF A PHASE IV TRIAL

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Introduction: While treatment response is the initial aim of therapy in major depressive disorder (MDD), disease remission is the ultimate goal. Symptom remission relative to response is associated with greater function, increased quality of life, and reduced risk of MDD relapse and recurrence. Antidepressant medications that can help patients achieve remission are an important component of MDD treatment. Vilazodone, a serotonin reuptake inhibitor and 5-HT<sub>1A</sub> receptor partial agonist, is approved by the US Food and Drug Administration for the treatment of MDD in adults. We evaluated the efficacy of vilazodone in achieving disease remission using various criteria. Methods: A post hoc analysis of response and remission data from a Phase IV, multicenter, randomized, 8-week double-blind, fixed-dose study (NCT01473394) comparing vilazodone 40 mg/day with placebo. The study comprised outpatients aged 18 to 70 years with DSM-IV-TR-defined MDD and a baseline total score  $\geq 26$  on the Montgomery-Asberg Depression Rating Scale (MADRS). The primary efficacy outcome was change from baseline to Week 8 in MADRS score; secondary and additional efficacy outcomes included the Clinical Global Impressions-Severity (CGI-S) and Hamilton Anxiety Rating Scale (HAMA). Post hoc analyses evaluated the percent of patients achieving depression symptom remission ( $\text{MADRS} \leq 10$ ), complete remission ( $\text{MADRS} \leq 5$ ), anxiety symptom remission ( $\text{HAMA} \leq 7$ ), and combined depression/anxiety symptom remission ( $\text{MADRS} \leq 10 + \text{HAMA} \leq 7$ ). Overall disease remission was also assessed ( $\text{CGI-S} = 1$ ). Additional analyses evaluated outcomes in patients with greater depression severity (baseline  $\text{MADRS} \geq 30$ ). Odds ratios (OR) and number needed to treat (NNT) were determined. Results: The intent-to-treat (ITT) population comprised 252 placebo and 253 vilazodone patients. At Week 8, a significantly greater percentage of vilazodone patients compared with placebo patients achieved MADRS remission (34% vs 22%;  $\text{OR} = 1.82$ ;  $P < .01$ ;  $\text{NNT} = 9$ ) and complete remission (18% vs 8%;  $\text{OR} = 2.42$ ;  $P < .01$ ;  $\text{NNT} = 10$ ). A greater proportion of vilazodone patients relative to placebo patients met criteria for HAMA remission (49% vs 35%;  $\text{OR} = 1.82$ ;  $P < .01$ ) and combined MADRS/HAMA remission (32% vs 20%;

OR=1.84;  $P<.01$ ). These results were supported by higher rates of overall disease remission as assessed by CGI-S (24% vs 12%; OR=2.41;  $P<.001$ ). In patients with greater baseline depression severity (MADRS $\geq$ 30), statistically significant results were seen on all remission outcome assessments for vilazodone vs placebo ( $P<.01$ , all outcomes), with larger ORs relative to the overall population (OR range: 1.92-3.46). Conclusions: These post hoc analyses suggest that vilazodone 40 mg/day is effective in achieving depression and anxiety symptom remission in adult patients with MDD. The remission benefits of vilazodone were seen in both the overall MDD population and those patients with greater severity of depression.

### **Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the efficacy of vilazodone treatment in achieving symptom remission in patients with major depressive disorder.
- At the conclusion of this session, the participant should be able to understand efficacy of vilazodone in patients with greater symptom severity.

**Source of Funding:** Supported by funding from Forest Laboratories, Inc.

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### **CLINICAL RELEVANCE OF LEVOMILNACIPRAN ER TREATMENT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: IMPROVEMENTS IN FUNCTIONAL IMPAIRMENT CATEGORIES**

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*<sup>1</sup>Florida Clinical Research Center, LLC, <sup>2</sup>Forest Research Institute, <sup>3</sup>Prescott Medical Communications Group*

**Introduction:** Major depressive disorder (MDD) is associated with impaired functioning at work and home, and social isolation. Residual functional impairment is common after antidepressant treatment and increases disability and risk of relapse. Medications that improve functional impairment associated with depression may play an important role in the management of MDD. Levomilnacipran extended-release (ER), a potent and selective serotonin and norepinephrine reuptake inhibitor, is FDA-approved for the treatment of MDD in adults. In phase II/III studies, functional impairment in MDD patients was assessed using the Sheehan Disability Scale (SDS). A previous analysis of these studies showed significantly greater mean improvements in functional impairment for levomilnacipran ER vs placebo on all 3 SDS Items (representing domains of work, social life, and family/home). This post hoc analysis explores shifts from greater severity of functional impairment at baseline to less severity at end of treatment (EOT) in patients treated with levomilnacipran ER vs placebo. **Methods:** Data were pooled from 2 fixed- and 3 flexible-dose randomized, double-blind, placebo-controlled trials of 8 or 10 weeks' duration of levomilnacipran ER 40-120 mg/day vs placebo in adult patients with MDD. Proportions of patients that shifted from moderate-to-high baseline impairment (score  $\geq$ 4) to mild-to-no impairment (score  $\leq$ 3) at EOT were assessed for each SDS item. Proportions of patients shifting from marked-to-high (score  $\geq$ 7) at baseline to moderate-to-no (score  $\leq$ 6) impairment at EOT also were assessed. **Results:** More levomilnacipran ER vs placebo patients achieved categorical SDS improvement. On the Work Item, a greater percentage of levomilnacipran ER vs placebo patients improved from moderate-to-high baseline impairment ( $\geq$ 4) to mild-to-no impairment ( $\leq$ 3) at EOT (55% vs 40%, odds ratio [OR]=1.96,  $P<.0001$ ); more levomilnacipran ER vs placebo patients with marked-to-high baseline impairment ( $\geq$ 7) had

moderate-to-no ( $\leq 6$ ) impairment at EOT (73% vs 64%, OR=1.81,  $P<.0001$ ). On the Social Item, higher proportions of levomilnacipran ER vs placebo patients improved from moderate-to-high impairment at baseline to mild-to-no impairment at EOT (48% vs 37%, OR=1.73,  $P<.0001$ ), and from marked-to-high impairment at baseline to moderate-to-no impairment at EOT (68% vs 59%, OR=1.61,  $P<.0001$ ). On the Family/Home Item, greater percentages of levomilnacipran ER patients relative to placebo shifted from moderate-to-severe impairment at baseline to mild-to-no impairment at EOT (51% vs 39%, OR=1.72,  $P<.0001$ ), and from marked-to-high impairment at baseline to moderate-to-no impairment at EOT (73% vs 65%, OR=1.47,  $P=.0027$ ). Conclusions: These results suggest that in adult patients with MDD, levomilnacipran ER treatment is associated with greater improvements than placebo across all SDS-measured functional domains of work, social, and family/home life.

### **Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the effect of levomilnacipran ER treatment versus placebo on SDS-measured domains of work, social, and family/home life in adult patients with MDD.
- At the conclusion of this session, the participant should be able to discuss shifts from greater severity of functional impairment at baseline to less severity at EOT in MDD patients treated with levomilnacipran ER relative to placebo.

**Source of Funding:** This study was funded by Forest Laboratories, Inc.

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### **LEVOMILNACIPRAN INHIBITS BOTH NOREPINEPHRINE AND SEROTONIN REUPTAKE ACROSS THE CLINICAL DOSE RANGE**

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Forest Research Institute*

**Objective:** Levomilnacipran extended-release (ER) is a potent and selective SNRI approved for the treatment of major depressive disorder (MDD) in adults. In vitro, levomilnacipran ER shows greater potency for inhibition of NE relative to 5-HT reuptake. The objective of this analysis was to characterize the pharmacokinetic (PK) profile of levomilnacipran ER 40, 80, and 120 mg/d and to use the PK data to estimate 5-HT and NE reuptake inhibition over the levomilnacipran ER dose range. **Methods:** PK data were collected from approximately 15% of adult patients with MDD who participated in an 8-week placebo-controlled, fixed-dosed trial of levomilnacipran ER 40, 80, and 120 mg/day. Blood samples were collected predose, and at 2, 4, 6, 8, 12, and 24 hours postdose. Plasma samples were analyzed using a validated LC-MS/MS method. To evaluate 5-HT and NE inhibition over the levomilnacipran ER clinical dose range, unbound levomilnacipran ER plasma concentrations obtained over a 24-hour period were plotted against previously determined in vitro 5-HT and NE reuptake inhibition profiles, which had been generated using human recombinant transporters expressed in HEK cells. **Results:**

Levomilnacipran steady state PK profiles were linear and dose proportional following oral administration. The  $C_{max}$  was 92.8 ng/mL, 180.4 ng/mL, and 297.2 ng/mL, for the 40, 80, and 120-mg doses. The average plasma concentrations at steady state for levomilnacipran ER were 63.3 ng/mL for 40 mg/day, 122.3 ng/mL for 80 mg/day, and 199.9 ng/mL for 120 mg/day. The average unbound plasma concentrations for levomilnacipran that were reached in MDD patients treated with levomilnacipran ER 40, 80, or 120 mg/day exceeded the concentration which

showed 90% and 80% inhibition of NE and of 5-HT reuptake, respectively, in vitro. Conclusion: These data suggest that levomilnacipran ER strongly inhibits both NE and 5-HT across the clinically effective dose range.

### **Learning Objectives:**

- At the conclusion of this session, participants should be able to identify the pharmacokinetic profile of levomilnacipran ER 40, 80, and 120 mg/day.
- In addition, participants should be able to use pharmacokinetic and in vitro pharmacology data to estimate 5-HT and NE reuptake inhibition over the levomilnacipran ER dose range.

**Source of Funding:** This study has been funded by Forest Laboratories, Inc.

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### **INCREASED ACC AND STRIATAL TOTAL CHOLINE LEVELS IN ADOLESCENT DEPRESSION**

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**Background** Adolescent major depression (MDD) is a highly heterogeneous disorder. Addressing this, our group has investigated anhedonia, a core symptom of depression, quantitatively. Our previous findings have shown that anhedonia –the reduced capacity to experience pleasure– is highly variable among adolescents with MDD. Additionally, we have documented a relationship between anhedonia and increased inflammation. Extending this work, we examined the relationship between total choline (tCho), a measure of membrane metabolism, and anhedonia in the anterior cingulate cortex (ACC) and striatum. Specifically, we expected increased tCho as a biomarker for lipid peroxidation, often a consequence of oxidative stress and inflammatory processes.

**Methods** **Patient Population** Our sample consisted of 30 MDD subjects, ages 12-20, diagnosed via the Kiddie-Schedule for Affective Disorders and Schizophrenia. All subjects had an episode duration  $\geq 6$  weeks and Children's Depression Rating Scale-revised (CDRS-R) scores  $\geq 37$ . All subjects were psychotropic medication-free for  $> 3$  months.

**In Vivo tCho Measurements** tCho concentrations were measured in the ACC and striatum using proton magnetic spectroscopy (1H MRS) on a GE 3.0T "EXCITE" MR system with a standard quadrature single-channel head coil using the method of Duyn et al. (1993). Anhedonia Scores Severity was assessed by a sum of anhedonia-related items from the CDRS-R and Beck's Depression Inventory. This approach to quantifying anhedonia allows for the clinician- and self-rated assessments to contribute equally. Statistics Pearson correlations, controlling for age and gender, were used to assess the relationship between tCho concentrations and anhedonia scores.

**Results** Among adolescents with MDD, anhedonia was positively correlated with tCho concentrations in the ACC ( $R = 0.41$ ,  $p < .03$ ). Furthermore, anhedonia scores were associated with greater increased tCho concentrations in the left putamen ( $R = 0.44$ ,  $p < .04$ ) and trended towards significance in the left caudate ( $R = 0.38$ ,  $p = .07$ )

**Conclusions** Our results are consistent with our previous findings supporting the role of inflammatory processes contributing to the biological underpinnings of anhedonia. These data further support the need for a dimensional investigative approach in the study of major depression.

**References:** 1. Gabbay V et al. The kynurenine pathway in adolescent depression: Preliminary findings from a proton MR spectroscopy study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010 (43):

37-44. 2. Duyn, J et al. Multisection proton MR spectroscopic imaging of the brain. *Radiology*, 1993 (188): 277-82.

### **Learning Objectives:**

- To understand the alterations in striatal and ACC tCho associated with adolescent MDD.
- To understand the importance of a dimensional approach when investigating adolescent MDD.

**Source of Funding:** Funding: NIH (AT002395, AT004576, MH077072, MH077072-03S1, MH075895), Chrissy Rossi National Alliance for Research on Schizophrenia and Depression Award, Leon Levy and Anita Saltz Foundations.

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### **COGNITIVE DOMAINS IMPACTED BY VORTIOXETINE TREATMENT OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD)**

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*<sup>1</sup>Metis Cognition Ltd., <sup>2</sup>H. Lundbeck A/S*

**Objective:** Vortioxetine treatment improved the performance of elderly patients with MDD (NCT00811252) on the Digit Symbol Substitution Test (DSST) [1], which requires the integrity of several cognitive domains. To determine which domain, or domains, of cognition were affected, we used additional measures of specific cognitive skills in a second study (NCT01422213) [2]. These post-hoc analyses sought to evaluate the efficacy of 1 and 8 weeks of treatment with vortioxetine 10 or 20mg/day on the cognitive domains “executive function,” “attention/speed of processing” and “memory.” **Methods:** Data from a double-blind, randomized, fixed-dose, placebo-controlled, depression study were used. 602 eligible patients aged 18-65 years were randomized (1:1:1) to vortioxetine 10mg/day, vortioxetine 20mg/day, or placebo for 8 weeks of double-blind treatment. The following cognition variables were used to assess cognitive function at baseline, week 1 and week 8: DSST number of correct symbols, Rey Auditory Verbal Learning Test (RAVLT) acquisition and delayed recall, Trail Making Test (TMT) parts A and B, Stroop test congruent and incongruent, and Simple Reaction Time (SRT) and Choice Reaction Time (CRT) tests. These variables were standardized and used for constructing composite Z-scores for cognitive domains: the Stroop incongruent test and TMT B for executive function; the Stroop congruent test, TMT A, SRT and CRT for attention/speed of processing, and the RAVLT acquisition and delayed recall for memory. The composite Z-scores and DSST number of correct symbols were analyzed using a Mixed Model including terms for grouped site, baseline value, baseline value-by-visit interaction, and treatment-by-visit interaction. Estimated treatment differences were based on the Least Squares means for the treatment-by-visit interaction. Least Squares means were rescaled to ensure SD=1. **Results:** At week 1, separation of vortioxetine 20mg/day versus placebo was found for attention/speed of processing (composite Z-score=0.28; p=0.007) and DSST number of correct symbols (Z-score=0.22; p=0.033), and of vortioxetine 10mg/day for executive function (composite Z-score=0.21; p=0.0425). At week 8, vortioxetine 10mg/day and 20 mg/day separated from placebo for executive function and attention/speed of processing, with composite Z-scores ranging from 0.35 to 0.49 (all p<0.01). Composite Z-scores for memory were 0.31 (p=0.0036, 10mg/day) and 0.22 (p=0.0349, 20mg/day). Standardized effect sizes for DSST number of correct symbols were 0.51 (p<0.0001, 10mg/day) and 0.52 (p<0.0001, 20mg/day). **Conclusions:** Vortioxetine (10 and 20mg/day) improves cognitive performance across several domains,

including executive function, attention/speed of processing and memory. The positive effect on the DSST appears to be due to improvements on a number of cognitive skills. [1] Katona C, et al. *Int Clin Psychopharmacol* 2012;27:215-223. [2] Jacobsen PL, et al. 2013. Available at <http://www.psychiatry.org/learn/library--archives>

### Learning Objectives:

- To understand how outcome measures from cognitive tests can be grouped and analyzed by cognitive domain.
- To appreciate that vortioxetine can improve domains of cognitive function.

**Source of Funding:** This study was funded by the H. Lundbeck A/S and Takeda Pharmaceutical Company, Ltd.

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### **A HEAD-TO-HEAD, RANDOMIZED, COMPARISON STUDY OF VORTIOXETINE VS. ESCITALOPRAM IN PATIENTS WELL TREATED FOR MDD AND EXPERIENCING TREATMENT-EMERGENT SEXUAL DYSFUNCTION**

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Vortioxetine is an antidepressant agent approved in late 2013 for Major Depressive Disorder (MDD), with multimodal activity that combines direct modulation of serotonin (5-HT) receptor activity and inhibition of the 5-HT transporter.<sup>1</sup> The receptor profile, available preclinical data, and a pooled analysis of 7 short-term clinical trials of vortioxetine suggest limited impact on sexual dysfunction. Objective: To compare the effects of vortioxetine and escitalopram on sexual functioning in US patients with well treated MDD experiencing treatment-emergent sexual dysfunction (TESD) (NCT01364649). Methods: Patients with recent major depressive episodes who had responded to SSRI treatment but were experiencing TESD were randomized to vortioxetine or escitalopram for 8 weeks. All patients discontinued their current SSRI treatment and were switched to vortioxetine 10mg or escitalopram (10mg for week 1 and 20mg for week 2 of treatment). The dose of vortioxetine could be adjusted after week 2, 4, or 6, as judged by the investigator. The primary endpoint was change from baseline to week 8 in the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score using MMRM. Secondary endpoints included other CSFQ-14 assessments, as well as change in Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI) scale, and Profile of Mood States (POMS). Safety and tolerability was assessed throughout the trial by physical examination, vitals, laboratory evaluations, ECGs, and adverse event (AE) reports. RESULTS Of 447 patients enrolled (vortioxetine, n=225; escitalopram, n=222), 348 completed the 8-week study (vortioxetine, n=169 [75.1%]; escitalopram, n=179 [80.6%]). The primary analysis demonstrated that patients treated with vortioxetine experienced a significant improvement in CSFQ-14 total score, with a mean change difference of 2.2 points (95% CI: 0.48–4.02) after 8 weeks of treatment (P=0.013; MMRM) compared to escitalopram. More vortioxetine-treated patients were responders (change from baseline in CSFQ-14 total score >3; OR=1.51; P=0.06), and shifted to normal sexual functioning during the study (OR=1.37; P=0.112) as compared with escitalopram. Numerically similar responses on the MADRS, CGI, and POMS were observed between the two groups at the end of week 8. The AE profile for vortioxetine was similar to that seen in previous trials, with nausea, headache, and dizziness as the most common AEs.



Conclusions: Vortioxetine was statistically significantly superior to escitalopram in improving TESD, measured by change in CSFQ-14 total score at Week 8. More vortioxetine-treated patients demonstrated a clinically meaningful improvement in sexual functioning and shifted to normal sexual functioning during the study, compared to escitalopram. Both drugs maintained or slightly improved clinical efficacy from Baseline levels to end of treatment, with safety profiles similar to that seen in previous trials. Reference: Adell A. Lu-AA21004, a multimodal serotonergic agent, for the potential treatment of depression and anxiety. *IDrugs*. 2010;13(12):900-910.

### Learning Objectives:

- Understand the clinical efficacy and safety profile of vortioxetine in patients with MDD suffering TESD
- Compare the sexual function profile of vortioxetine with escitalopram in patients with mood disorders

**Source of Funding:** This study was funded by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S.

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### THE ROLE OF PRO-INFLAMMATORY CYTOKINES IN MODULATION OF ACTIVITY OF SEROTONINERGIC SYSTEM IN WOMEN WITH POSTPARTUM DEPRESSIVE SYMPTOMS AND IN ANIMAL MODELS OF DEPRESSION

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Educational Objectives: There is evidence that immuno-inflammatory, oxidative and nitrosative stress (IO&NS) pathways are involved in depression and staging of depression. Data show that knowing how IO&NS pathways cause depression will lead to new treatment approaches (1, 2).

Purpose: The aims of the paper is to elucidate the role of serotonergic system in peripheral and central cell signaling networks and their complex dynamic modulation of the IO&NS pathways that explain depression and staging of depression. Methods: These goals was achieved by using high throughput technologies to collect protein data from the blood of patients with depression and secondary depression. Serum concentration of: interleukin-1 (IL-1), IL-6, the soluble IL-6 receptor (sIL-6R), sgp 130 (the IL-6 signal transducing protein), the sIL-1R antagonist (sIL-RA), interferon (IFN)-gamma, plasma tryptophan and kynurenine were determined in 20 and 30 women with and without a lifetime history of major depression, respectively. Blood was collected 3-6 days before delivery and 1 and 3 days after delivery. On each occasion the women completed the Zung Depression Rating Scale (ZDS). In experimental studies prenatal stress (PS) model of depression were used. Studies were performed on four-month old Sprague-Dawley female and male rats subjected to PS. Depressive behavior of animals were estimated using forced swimming test. Brain (cortex and hippocampus) level of neurotransmitters: serotonin (5-

HT) and dopamine (DA) and their metabolites (5-HIAA; DOPAC, HVA) in correlation with spleen cytokines levels were estimated. Results: Depressive symptoms in the early puerperium were related to activation of inflammatory response (IL-6, sIL-RA) and to reduced plasma tryptophan level (human studies) in women suffered from a lifetime history of major depression. Depressive symptoms in correlation with decrease in activation of serotonergic system and increase in pro-inflammatory cytokines (IL-6, IFN-gamma) level were more escalate in female than male prenatally stressed rats. Conclusions: · The responses of IL-6 and sIL-RA following delivery are amplified in women who previously suffered from major depression. · Depression is accompanied by a sensitization of the inflammatory response system in correlation with decrease of activity of serotonergic system. · Our data will add some information to visualize the complex network architecture between neurotransmitter and immune systems in depression and delineate novel drug targets leading to the development of new approaches to treat and prevent depression.

### **Learning Objectives:**

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**Source of Funding:** This study was supported by the grant POIG.01.01.02-12-004/09-00

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### **ANTI-ANHEDONIC EFFECT OF KETAMINE AND ITS NEURAL CORRELATES IN MAJOR DEPRESSIVE DISORDER**

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An estimated 40% of patients with major depressive disorder (MDD) suffer from clinically significant anhedonia, the loss of enjoyment or desire towards a previously pleasurable activity. Critically, these patients have poorer treatment prognosis than their non-anhedonic counterparts. Furthermore, accumulating evidence suggests that standard treatments for depression have little efficacy in treating anhedonic symptomatology; there is currently no FDA approved treatment specifically for anhedonia. The noncompetitive NMDA receptor antagonist ketamine has shown remarkable consistency in rapidly ameliorating depressive symptoms in both unipolar and bipolar depression. However, it is unknown whether ketamine possesses specific anti-anhedonic efficacy in humans. In an open label single ketamine infusion study with adjunctive daily randomized placebo controlled riluzole treatment, beginning four hours post-ketamine infusion, we assessed the anti-anhedonic effects of ketamine and riluzole in a sample of (N=52) treatment-resistant MDD patients over 28 days. We evaluated levels of anhedonia using the Snaith-Hamilton Pleasure Scale (SHAPS). In a subsample of these patients (N=20) we also conducted [18F] fluorodeoxyglucose positron emission tomography (PET) scans at baseline and four hours post-infusion. We regressed changes in anhedonia levels onto difference images to identify mediating neural mechanisms of ketamine's anti-anhedonic capacity. Our results indicate that,

prior to riluzole randomization, levels of anhedonia were significantly reduced following ketamine (main effect of time,  $F(4,129) = 8.31, p < .001$ ), with significant Bonferroni corrected differences between baseline levels of anhedonia at 40 ( $t(169) = 5.68, p < .001$ ) through 230 ( $t(101) = 3.01, p = .03$ ) minutes post-infusion. However, when controlling for levels of depression, these results were no longer significant ( $F(4,163) = 1.62, p = .17$ ). Examining the post-riluzole administration phase (days 1 to 28) when controlling for baseline anhedonia levels, there was no main effect of drug ( $F(1,51) = 0.20, p = .66$ ) nor an interaction between drug and time ( $F(27,611) = 1.20, p = .22$ ), indicating that riluzole was not better than placebo at alleviating anhedonia. However, when including baseline in a model without drug, there was a significant main effect of time ( $F(28,582) = 2.79, p < .001$ ), where improvement from baseline due to ketamine extended to day 6. This main effect was at trend level when controlling for levels of depression ( $F(28,665) = 1.38, p = .09$ ), indicating tentative focal amelioration of anhedonia levels by ketamine independent of improvements in other depressive symptomatology. Our PET analyses indicated a role for the hippocampal formation in mediating the anti-anhedonic effect of ketamine (PWE = .017); relative to baseline, individuals with greatest anti-anhedonic response at 230 minutes post-infusion had the largest increase in glucose metabolism in the subiculum. This result was also present when the variance associated with change in other depressive symptomatology was controlled (PWE = .027). Our results add increasing weight to the potential of NMDA receptor antagonists in the treatment of depression.

### Learning Objectives:

- The aim of this investigation was to assess whether ketamine exerts rapid acting effects on levels of anhedonia in patients diagnosed with major depressive disorder.
- The secondary aim was to examine what the underlying neurobiology of this effect may be.

**Source of Funding:** Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; grant number 04-M-0222), by a National Alliance for Research on Schizophrenia and Depression Award to CAZ, and by a Wellcome Trust NIH PhD studentship (WT095465) to NL. A patent application for the use of ketamine in depression has been submitted listing CAZ among the inventors; he has assigned his rights on the patent to the U.S. government, but will share a percentage of any royalties that may be received by the government. All other authors have no conflicts of interest to disclose, financial or otherwise.

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### **ALKS 5461, A NOVEL OPIOID MODULATOR AS ADJUNCTIVE TREATMENT FOR DEPRESSION: ADDRESSING ABUSE POTENTIAL, SAFETY AND EFFICACY**

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Background Use of opioids for mood syndromes pre-dates the antidepressant era, but is rare in modern practice due to concerns about abuse and dependence. ALKS 5461 is a co-formulation of buprenorphine (BUP), a partial  $\mu$ -opioid agonist, and samidorphan, a counter-acting  $\mu$ -opioid

antagonist, in development as adjunctive therapy for inadequate response to antidepressants in major depressive disorder (MDD). The early clinical development program aimed to identify the optimal ratio of BUP and samidorphan that would yield a potentially safe and non-abusable opioid modulator; and subsequently the safety and efficacy of the selected dose ratio was evaluated in MDD patients. Methods A Phase 1, double-blind, single-dose, placebo (PBO)-controlled study was conducted in recreational opiate users (N=12). Subjects were randomized to a treatment sequence including sublingual BUP (8 mg) + samidorphan (PBO, 1, 4, 8, or 16 mg) in an adaptive dosing strategy. Pharmacodynamic blockade was defined as no significant pre-post change on objective (pupil miosis) and subjective (standard drug-liking scales) measures. A subsequent Phase 2, PBO-controlled sequential parallel comparison design (SPCD) study with two 4-week treatment stages was conducted in patients with MDD and inadequate response to antidepressants (N=142). Treatment groups included 2 mg/2 mg or 8 mg/8 mg of BUP/samidorphan vs. matching PBO. Safety and tolerability was assessed in both studies. Results In recreational opiate users, 8 mg BUP + 1 mg or 4 mg of samidorphan substantially diminished opioid effects of BUP on all primary measures. At the 1:1 and 1:2 ratios of BUP/samidorphan (8 mg/ 8 mg and 8 mg/16 mg) the drug liking and miosis signals were abolished through 24 hours of post-dose assessment. In patients with MDD, stage-combined analyses found significantly greater reduction of depressive symptoms on both the 17-Item Hamilton Depression Rating Scale (HAM-D17; p=0.006) and the Montgomery-Asberg Depression Rating Scale (MADRS; p=0.001) for ALKS 5461 2 mg/2 mg vs. PBO. Consistent findings in response and remission rates were also observed for ALKS 5461 2 mg/2 mg vs. PBO. Most common AEs across both studies were nausea, vomiting and sedation, typical of opioid therapy, with no evidence of opiate withdrawal upon treatment discontinuation. Conclusions Samidorphan simultaneously administered with BUP in a 1:1 dose ratio was safe and well tolerated, and produced rapid, long-lasting blockade of  $\mu$ -opioid agonist effects in recreational opiate users, indicating a potential absence of abuse potential in the appropriate population. In patients with MDD, adjunctive ALKS 5461 demonstrated significant and clinically robust improvement in depressive symptoms in patients with inadequate antidepressant response. Findings require replication in phase 3. ALKS 5461 combines BUP and samidorphan in a ratio that displays antidepressant efficacy while limiting abuse potential, suggesting opioid modulation may be a novel and important new treatment approach for this serious, chronic disease. References: 1. Emrich HM, et al. Lancet. 1982; 2:709

### **Learning Objectives:**

- Learn about pharmacodynamic endpoints in clinical research.
- Learn about the efficacy and safety of ALKS 5461 in MDD.

**Source of Funding:** Financial support: NIDA N01DA-6-8867 and Alkermes, Inc.

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## **EFFECTS OF VILAZODONE ON SEXUAL DYSFUNCTION IN MAJOR DEPRESSIVE DISORDER: A RANDOMIZED, DOUBLE-BLIND TRIAL WITH PLACEBO AND ACTIVE CONTROLS**

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Introduction: Vilazodone, a serotonin reuptake inhibitor and 5-HT<sub>1A</sub> receptor partial agonist, is approved for the treatment of major depressive disorder (MDD) in adults. A recent positive Phase IV study (NCT01473394) supported the efficacy of vilazodone 20 and 40 mg/day (VLZ 20, VLZ 40) in the treatment of MDD; citalopram 40 mg/day (CIT) was used to evaluate assay sensitivity. All active treatment groups showed statistically significant improvement versus placebo (PBO) on the Montgomery-Asberg Depression Rating Scale (MADRS), the primary efficacy measure. Both MDD and treatment with serotonergic antidepressants can be associated with sexual dysfunction. Post hoc analyses characterized sexual functioning in patients with MDD treated with PBO, VLZ 20, VLZ 40, or CIT. Methods: A 10-week multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose study compared VLZ 20, VLZ 40, and CIT with PBO (NCT01473381). The study comprised male and female outpatients aged 18 to 70 years who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD and had a baseline MADRS score  $\geq 26$ . Sexual functioning was assessed using the Changes in Sexual Functioning Questionnaire (CSFQ) in 1147 patients (PBO=264, VLZ 20=267, VLZ 40=259, CIT=257) with a baseline and  $\geq 1$  postbaseline CSFQ score. Sexual dysfunction was defined as CSFQ scores  $\leq 47$  for men and  $\leq 41$  for women. Post hoc analyses evaluated mean change in CSFQ score from baseline to end of treatment (EOT). The percentage of patients with normal sexual function at baseline who met sexual dysfunction criteria at 2 consecutive double-blind visits and the percentage with sexual dysfunction at baseline who had normal sexual function at EOT were also analyzed. Results: A high percentage of patients in all treatment groups had baseline sexual dysfunction: men (PBO=50%, VLZ 20=54%, VLZ 40=55%, CIT=52%); women (PBO=62%, VLZ 20=64%, VLZ 40=70%, CIT 67%). Baseline CSFQ scores were approximately 42 for all treatment groups. Least squares mean increase in CSFQ scores at EOT was 2.5 for PBO, 2.6 for VLZ 20, 2.0 for VLZ 40, 1.5 for CIT. In patients with normal baseline sexual function, 12% of PBO and 16%, 15%, and 17% of VLZ 20, VLZ 40, and CIT patients, respectively, met criteria for sexual dysfunction at 2 consecutive double-blind visits. In patients with baseline sexual dysfunction, 33% of PBO, and 35%, 30%, and 28% of VLZ 20, VLZ 40, and CIT patients improved to normal sexual function at EOT. Conclusions: In a post hoc analysis of a Phase IV trial, the rates of sexual dysfunction were similar for PBO-, VLZ-, and CIT-treated patients. Mean CSFQ scores increased in all treatment groups, however, CSFQ score increases were numerically greater in both VLZ groups compared with CIT.

### **Learning Objectives:**

- Evaluate the effects of vilazodone and citalopram treatment on sexual function in patients with MDD.
- Understand effects of vilazodone on patients with normal baseline sexual function and with baseline sexual dysfunction.

**Source of Funding:** Supported by funding from Forest Laboratories, Inc.

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**An 8-Week Randomized, Double-Blind Trial Comparing Efficacy, Safety And Tolerability Of Three Vilazodone Dose Initiation Strategies Following Switch From SSRIs or SNRIs In Major Depressive Disorder**

**Introduction:** Vilazodone, a selective and potent serotonin (5-HT) reuptake inhibitor and 5HT1a partial agonist is approved for major depressive disorder (MDD) in adults. The primary objective of the study was to compare the efficacy and tolerability of switching to one of three different starting doses of vilazodone from SSRIs or SSNRIs in adult subjects with MDD. **Methods:** This was an 8-week, randomized, double blind, parallel group, 3-arm trial to compare 10 mg/d, 20 mg/d and 40 mg/d as starting doses of vilazodone, with a final dose of 40 mg/d in adults with MDD (NCT02015546). There was no washout phase, prior SSRI/SNRI medications were stopped at the baseline visit and vilazodone was started the next day. The 10 mg/d and 20 mg/d starting dose was increased to 40 mg/d by week 3 and week 1 respectively and the 40 mg/d initiation dose continued unchanged. The primary efficacy measure was change from baseline at Week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) total score, compared between the 3 starting dose groups. The secondary efficacy measures included the Discontinuation- Emergent Sign and Symptoms Scale (DESS). Safety measures included spontaneously reported adverse events, vital signs and laboratory tests. Multivariate tests were used for statistical analysis. **Results:** 71 subjects were randomized (n=20 in each group) and 60 subjects completed the study. Overall, there was a significant reduction in mean $\pm$  SEM in MADRS score from baseline ( $26.08 \pm 1.1$ ) to week 8 ( $9.86 \pm 1.2$ ) in the 3 groups combined ( $p < .001$ ). There were no significant differences between the three vilazodone dose initiation groups in mean changes in MADRS ( $p = 0.95$ ), CGI-S ( $p = 0.83$ ), CGI-I ( $p = 0.51$ ) or HAM-A scores ( $p = 0.61$ ). DESS scores from baseline ( $5.9 \pm 9.9$ ) to Week 8 ( $2.2 \pm 5.5$ ,  $p < 0.01$ ). Statistical significant changes in DESS scores were not observed 1 week after discontinuing vilazodone ( $p = 0.32$ ). There were no significant differences between the three vilazodone starting dose groups in changes in DESS scores 1 week after discontinuing vilazodone ( $p = 0.50$ ). ASEX scores showed decrease from baseline ( $17.5 \pm 5.2$ ) to end point ( $15.9 \pm 6.3$ ,  $p = 0.01$ ). Dry mouth (n=55), nausea (n=10) and diarrhea (n=5) were most common side effects, with diarrhea reported in 5 subjects in 40 mg/d initiation group. There were no serious adverse events reported. **Conclusions:** There were no meaningful differences in efficacy or tolerability between the 3 different dose initiation strategies with vilazodone, however, diarrhea appeared to be more frequently reported with 40 mg/d dose. No significant discontinuation emergent symptoms were observed with vilazodone after one week. Given the modest sample size, larger studies are required to confirm our findings.

### Learning Objectives:

- To compare the safety and tolerability of switching to three different doses of vilazodone (10 mg/d, 20 mg/d, 40 mg/d) from equivalent dose range of generic SSRIs or SSNRIs in patients with MDD.
- To compare the efficacy of switching to three different doses of vilazodone (10 mg/d, 20 mg/d, 40 mg/d) from equivalent dose range of generic SSRIs or SSNRIs in patients with MDD.
- To examine the rate and extent of discontinuation syndrome following the switch from generic SSRI and SNRI to three doses of vilazodone.

- To compare the rate and extent of discontinuation symptoms following abrupt discontinuation versus a 1-week taper of vilazodone at the end of the 8-week trial.

**Source of Funding:** Funding: This study was supported by Forest Research Institute through an Investigator Initiated Award

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**ADJUNCTIVE LANICEMINE (AZD6765) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND A HISTORY OF INADEQUATE RESPONSE TO ANTIDEPRESSANTS: POST-HOC ANALYSES OF A RANDOMIZED, PLACEBO CONTROLLED STUDY (PURSUIT)**

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Objective: Study 9(1) and Study 31(2) (PURSUIT) were Phase IIb, multicenter, randomized, double-blind, placebo-controlled studies of adjunctive lanicemine in patients with MDD and a history of inadequate response to prior treatments. In Study 9 (n=152), LS mean change in MADRS score at Week 3 was significantly greater for 100 mg and 150 mg lanicemine than placebo.(1) In Study 31 (n=302), LS mean change in MADRS score at Week 6 was not significantly different for 50 mg or 100 mg lanicemine versus placebo.(2) Post-hoc analyses and literature review investigated explanations for disparity between the studies.(1,2) Methods: Post-hoc analyses assessed effects of study design differences, including drug exposure analysis by population pharmacokinetic (PK) approach, baseline severity of MDD, history of failure to respond to antidepressants, and study center experience. Results: Studies 9 and 31 at Week 4 (only shared assessment point) showed similar MADRS score changes in adjunctive lanicemine 100 mg groups (-13.3 vs -13.8), but greater MADRS change for adjunctive placebo in Study 31 than Study 9 (-13.9 vs -9.1). Variance (SD) in MADRS change from baseline was also higher in Study 31. Mean PK drug exposure (area under curve) for 100 mg was similar between the studies. Lanicemine-placebo MADRS score differences in Study 31 were greater when selecting for (1) patients with greater level of treatment resistance (based on dose and treatment duration); (2) higher baseline severity; (3) shorter total duration of double-blind and follow-up periods; and (4) sites experienced in treatment-resistant depression and infusions. In patient subgroups with greater level of treatment resistance on lanicemine 50 mg (n=57), 100 mg (n=51), or placebo (n=50), MADRS change from baseline (LSM±SE) at Week 6 was -16.2±1.4, -20.4±1.6, and -9.0±1.5, respectively. Discussion: Post-hoc analyses of 2 adjunctive lanicemine studies (Study 9 and Study 31) identified potential explanations for disparity in outcomes, arising in part from high placebo response rate in Study 31. On literature review, only 21.1% of trials of approved antidepressants with a high placebo response (ie, >30% mean score change [39% in Study 31]) showed statistical superiority over placebo. Baseline severity and duration of double-blind period also influenced study significance in antidepressant trials. More stringent selection of patients who failed to respond to multiple prior treatments might have enhanced detection of a treatment effect by limiting placebo response in Study 31.

**References:**

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### **Learning Objectives:**

- Most Phase II and III trials of approved antidepressants do not demonstrate statistical superiority of drug over placebo. Placebo response is a key factor in assay sensitivity of clinical trials. These post-hoc analyses provide insights relevant for study design.

**Source of Funding:** AstraZeneca

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### **THE ROSENBERG HASSMAN MOOD SCALE - AN UPDATE ON THE DEVELOPMENT OF THIS DEPRESSION RATING SCALE WITH FEEDBACK FROM 50 PATIENTS**

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Depression scales are used as primary efficacy measures in clinical research studies. I will briefly look at the commonly used scales as well as the Rosenberg Hassman Mood Scale (RHMS) using evidenced-based information about the ideal scale. Detailed information on RHMS development will be presented. The RHMS is based on the hypothesis that symptom frequency is, by itself, an objective measure of both disease severity and change in disease severity. This frequency hypothesis was generated as a result of the diagnostic requirements that symptoms of a Major Depressive Episode (MDE) be present “most days, most of the day,” and from other medical fields where patients are assessed by asking “how often have you had angina, diarrhea, etc.?” Our review with experts determined that distress and impairment must also be measured and ideally measured in a way that avoids systematic errors due to unemployment and vacations, etc. Most experts prefer the use of a 7 day recall. Finally, since the RHMS is a psychological test, incorporating a way to validate answers the way that it is done in other psychological tests was felt worthy of consideration. The RHMS has incorporated the following concepts from the literature: 1. People are able to discriminate into 5 to 9 categories as discussed in “The Magical Number is Seven, Plus or Minus Two.” 2. The use of only 5 response options reduces reliability by 12% compared with 7 to 10 response options. 3. Response options should unequivocally demonstrate the continuum to evaluate, be continuous, and have interval constancy. 4. Response Options should have the same number of letters. 5. ‘Double-barreled’ (confounded) questions are to be avoided. Our first two rounds of patient input accomplished the following: From among nine response option formats that adhered to the above criteria, one was preferred with an effect size of 0.59. Mixed Modelling was used to conduct ANOVAs on the responses. We reduced 334 potential word/phrase synonyms down to 228 in 23 categories. 68 patients completed the survey. A cutoff score of 65% of patients endorsing the word/phrase as a synonym was used to determine that the word/phrase be included in the RHMS. This report will present new data from the third stage of patient input; the computerized self-administration of the



RHMS by 50 patients. The RHMS showed good test retest reliability (0.86). Furthermore two global ratings of depression correlated well with RHMS, both correlating 0.65 on visit 1, and 0.67/0.68 on visit 2. These 50 patients were given a 27 item questionnaire. The data will be presented. The five areas they most strongly agreed with were: 1. The RHMS will cause no increase in the risk of committing suicide 2. The RHMS is very easy to use 3. The RHMS vocabulary is easy to understand 4. Overall the RHMS is excellent (as opposed to poor) 5. I definitely would take the RHMS again if I were able to track my scores from session to session. The RHMS has since been converted from a lap-top based scale into a web-based scale. In addition to the new data noted above, another stage of validation is currently underway and will be reported on as well. This involves intra-patient correlations between the RHMS and established depression scales including the Hamilton and the Montgomery-Asberg.

### Learning Objectives:

- From a scientific perspective, what are the strengths and weaknesses of existing depression rating scales? From a scientific perspective, what are the strengths and weaknesses of the Rosenberg Hassman Mood Scale?

**Source of Funding:** Self-Funded

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### **EFFICACY OF VORTIOXETINE VS PLACEBO IN ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD): META-ANALYSES OF MADRS SINGLE ITEMS FROM 9 SHORT-TERM STUDIES**

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**Background:** Vortioxetine was approved in the United States and Europe in 2013 for the treatment of adults with MDD. Its mechanism of action of vortioxetine is thought to be multimodal: direct modulation of receptor activity and inhibition of the serotonin transporter.<sup>1,2</sup>  
**Objective:** To evaluate the efficacy of vortioxetine 5–20mg/day vs placebo in clinical symptoms of depression in adults with MDD, as assessed by change from baseline (CFB) in the 10 items of the Montgomery-Åsberg Depression Rating Scale (MADRS). **Methods:** Analyses were based on data from 10 randomized, double-blind, short-term, placebo-controlled studies (9 adult, 1 elderly) in MDD patients in the NDA. All eligible patients met DSM-IV criteria for a major depressive episode and had a baseline MADRS total score (TS) of >22, 26, or 30. CFB to study endpoint (week 6/8) on MADRS TS and each MADRS single item was analyzed for each trial (full analysis set, mixed model for repeated measures analysis). Results from each of the 9 trials in adults were used for a random effects meta-analysis for MADRS TS and for each item.  
**Results:** The meta-analysis included 3203 patients (1215 placebo, 714 vortioxetine 5mg; 571 10mg; 344 15mg; 359 20mg). A consistent dose response was observed across the therapeutic dose range of 5 to 20mg in each individual trials where >1 dose was studied; this was reflected in the meta-analysis. The mean difference from placebo for vortioxetine in CFB to week 6/8 in MADRS TS was –2.6 (5mg; P<0.01), –3.5 (10mg; P<0.001), –2.6 (15mg; P=NS), and –4.5 points (20mg; P<0.001). A dose-related improvement on all MADRS single items was observed for vortioxetine (5, 10, 15, and 20mg, respectively) versus placebo (Apparent Sadness: –0.35, –0.48, –0.41, and –0.64; Reported Sadness: –0.3, –0.49, –0.46, and –0.66; Inner Tension: –0.24, –0.43, –0.21, and –0.4; Reduced Sleep: –0.35, –0.39, –0.18, and –0.48; Reduced Appetite: –0.19,

–0.23, –0.17, and –0.29; Concentration Difficulties: –0.23, –0.22, –0.37, and –0.48; Lassitude: –0.25, –0.3, –0.26, and –0.41; Inability to Feel: –0.33, –0.4, –0.24, and –0.52; Pessimistic Thoughts: –0.22, –0.34, –0.21, and –0.53; and Suicidal Thoughts: –0.08; –0.11, –0.14, and –0.14). Similar results were found in the study of elderly patients. Conclusion: This meta-analysis found that vortioxetine had a broad antidepressant effect, as shown by improvements on all individual MADRS items, and that the magnitude of the overall effect was dose-dependent, increasing with dose.

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#### Learning Objectives:

- To evaluate the broad clinical efficacy profile of vortioxetine in adults with MDD, as evaluated by assessment of the MADRS total score and single items.
- To understand the dose-dependent clinical effect of vortioxetine in adults with MDD.

**Source of Funding:** This study was funded by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S.

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#### MTOR SIGNALING CORRELATES WITH TREATMENT RESPONSE TO KETAMINE IN A PRECLINICAL MODEL OF TREATMENT RESISTANT DEPRESSION

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Background: Ketamine, an NMDA receptor antagonist and known anti-inflammatory agent, has rapid therapeutic effects in patients with intractable forms of depression. Clinical and preclinical studies are providing evidence that ketamine significantly reduces depressive symptomatology in severely treatment resistant patients; however, mechanisms mediating this therapeutic effect and biomarkers of response are not well understood. Studies with the potential to inform on differential antidepressant responses to ketamine administration in treatment resistant depression are urgently needed. Aberrant activation of the hypothalamic-pituitary-adrenal (HPA) axis and an irregular inflammatory profile have been observed in such patients. Mammalian target of rapamycin (mTOR) and neurotrophin signaling are suspected mechanisms of this rapid antidepressant response. Methods: We investigated the antidepressant effects of ketamine in a preclinical model of antidepressant resistance induced through daily injections of adrenocorticotrophic hormone (ACTH) (100µg/d) for 14 days. Animals received ketamine hydrochloride (KET) (10mg/kg) or control vehicle saline (SAL) (0.9%) 1h prior to behavioral tests. Behavioral tests included an open field test (day 14) and the Porsolt forced swim test (day 15). 30 min post FST animals were humanely euthanized and C-reactive protein (CRP) and mTOR, GSK, AKT, TrkB, and BDNF protein levels were measured in plasma and prefrontal cortex (PFC), respectively. Results: A significant decrease in immobility was observed in control animals treated with KET. A divergent response profile was observed in ACTH-KET treated

animals. ACTH animals were grouped into responders '[+]' and non-responders '[-]'. We observed a significant reduction in mTOR signaling in the PFC of SAL-KET and ACTH-KET[+] following exposure to the FST. This was not observed in ACTH/KET[-] animals. Differences in plasma CRP levels were also observed across groups. Conclusions: These findings suggest that antidepressant-resistant animals demonstrate differential antidepressant responses to ketamine. 'Efficacious' response was associated with elevated plasma CRP levels, reduced post-mortem levels of mTOR pathway proteins and elevated TrkB proteins in the PFC.

**Source of Funding:** State of Minnesota

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### **A NOVEL TRIAL DESIGN TO ASSESS RAPID AND SUSTAINED ANTIDEPRESSANT EFFECTS OF AN ORAL NR2B SPECIFIC NMDA RECEPTOR ANTAGONIST, CERC-301**

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There is a significant unmet medical need for rapidly acting treatment of subjects with severe major depressive disorder (MDD) who have not adequately responded to antidepressant therapy. Alternative therapies require weeks to achieve full efficacy, may have significant side effects and still fail in a high percentage of subjects. Furthermore, suicidal ideation is common in subjects with severe depression and is a risk for suicidal behavior. Rapid reduction of severe depression and suicidal ideation by pharmacological therapy is important to reduce the need for hospitalization and risk of self-harm and mortality. In addition, antidepressants with new mechanisms of action may successfully treat patients who have failed existing therapies, perhaps by acting synergistically with antidepressants primarily affecting monoamine systems.

Considerable clinical and preclinical evidence suggests that drugs that block the N-methyl-D-aspartate (NMDA) receptor complex result in a rapid onset of antidepressant response in animal models of depression and in patients who are resistant to available antidepressants. CERC-301 is a highly selective NMDA NR2B antagonist. A Phase IB placebo-controlled, crossover study of CERC-301 in five subjects with treatment-resistant depression showed promising results.

Subjects administered an intra-subject dose escalation of CERC-301 orally (from 4 mg/day to 8 mg/day) over 12 days improved on the 17-item Hamilton Depression Rating Scale (HDRS-17) and Beck Depression Inventory (BDI), although the Montgomery-Asberg Depression Rating Scale (MADRS) was unchanged. The current study uses a novel methodology, the Sequential Parallel Comparison Design (SPCD), to evaluate the antidepressant effect of CERC-301 during 28 days of treatment in subjects with MDD who are currently experiencing a severe depressive episode despite stable ongoing treatment with selective serotonin- or serotonin-norepinephrine reuptake inhibitors (SSRI or SNRI). The study population will be enriched for subjects that would benefit most from rapid onset, those with recent active suicidal ideation, but not a risk to themselves or others and are deemed appropriate for an out-patient study with careful safety surveillance. This will allow the study to focus on the antidepressant effects of CERC-301, but also explore effects on suicidal ideation. To explore rapid onset, the primary endpoint will be at 7 days, but effects over the 28 days of treatment will be examined as a secondary endpoint. In

order to combine assessment of rapid onset and sustained effect in the same study, the design is a new variant of SPCD, with two study periods of different durations (Period 1 [7 days] and Period 2 [28 days]). Period 1 and the first 7 days of Period 2 are analyzed using the established SPCD methodology. A secondary analysis of 28-day treatment periods for sustained effect will include pooled 28 day treatment data, excluding placebo responders of Period 1, in a staggered start design. This study design enables the evaluation of (1) the rapid onset of antidepressant effect, (2) the maintenance effect of the study drug, and (3) the drug vs. placebo effects across the two phases, by reducing the pooled placebo response using traditional SPCD methodology.

### **Learning Objectives:**

- Learn about a potential new agent for treatment of depression, an oral highly selective NMDA NR2B antagonist.
- Gain understanding of novel trial designs to evaluate rapid onset and sustained antidepressant effects.

**Source of Funding:** Cerecor, Inc.

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### **AN INTERNATIONAL STUDY OF THE GRID-HAMD: HAS IT FULFILLED ITS PROMISE?**

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**Introduction:** The GRID-HAMD1 provides a novel grid scoring structure that allows clinicians to rate severity and frequency as independent axes. The newly-formulated instrument also provides a structured interview guide and scoring conventions on the same page as each item. Finally, the GRID-HAMD presents revised anchor points for items that were problematic or inconsistently rated. The GRID-HAMD has now been available for five years and has been the major outcome measure for several large clinical trials. This poster presents the results of a survey of a global cohort of 74 highly trained and calibrated clinical interviewers who have collectively administered the GRID-HAMD 4850 times in global clinical trials. **Methods:** The survey included statements about the usability and ease of use of the GRID-HAMD, the new page layout, the revised item wordings and the grid format that were to be rated on a seven point scale from strongly disagree (1) to strongly agree (7). In addition, raters were asked to nominate the items they found most difficult to administer as well as those they found the easiest to administer, and to describe the reasons for these opinions. Finally, the questionnaire listed four statements asking raters to compare the GRID-HAMD with the SIGH-D, a widely-used version of the HAM-D (Williams, 1988), with a response from 1=GRID-HAMD to 7=SIGH-D. **Results:** The survey was completed by 60 of 74 (81%) raters. All respondents had at least three years' experience assessing depression and 2/3 are MDs or PhDs. About half (53%) live in Europe, 40% in the US, and the remaining in Russia or South Africa. For all items, respondents rated most frequently on the positive end of the scale. Tables will be presented listing the percentages that agree/disagree with each statement. Across all 8 items about usability and ease of use, agreement was strong (average % agreement= 75% for GRID; average % disagreement = 13% for GRID). In general, the unique grid format for rating items was well-accepted, with agreement

on the usefulness of this approach ranging from 72% to 85%. The vast majority of respondents to this survey agreed that the “symptom intensity levels are defined clearly” in the GRID-HAMD (82%). Raters overwhelmingly (87% agreement) endorsed the GRID-HAMD strategy of including scoring conventions on the same page as each item. However, finally, despite positive ratings for the GRID-HAMD throughout the survey, for each of the final three overall preference questions, respondents preferred the SIGH-D over the GRID-HAMD by a small margin. Conclusions: The GRID-HAMD is well accepted by clinical raters. Raters positively endorsed its new grid format with separate ratings for symptom intensity and frequency, as well as the new graphical layout, with each item, its interview questions, and its conventions, all on the same page. Also, its revised anchor points were endorsed as clearly defined and useful. Surprisingly, however, raters indicated an overall preference for the SIGH-D versus the GRID-HAMD.

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#### Learning Objectives:

- To gauge raters’ evaluation of the features of the new GRID-HAMD.
- To compare raters’ preferences between the GRID-HAMD and the SIGH-D.

**Source of Funding:** MedAvante

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### **VALIDATION OF THE YALE-BROWN OBSESSIVE COMPULSIVE SCALE MODIFIED FOR BINGE EATING TO SUPPORT USE IN CLINICAL TRIALS AS A MEASURE OF TREATMENT BENEFIT**

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**Objective:** The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), developed for obsessive compulsive disorder, has been used in clinical trials in a modified form (Y-BOCS-BE) to measure obsessive thoughts and compulsive behavior related to binge eating disorder (BED). We assess key Y-BOCS-BE properties to support its use as a measure of treatment benefit in clinical trials. **Method:** Psychometric properties of the Y-BOCS-BE were evaluated with data from a phase 2 randomized, double-blind, placebo-controlled study that evaluated 3 doses of an investigational treatment in adults with protocol-defined moderate-to-severe BED. Response distributions were examined to identify any distribution anomalies (floor/ceiling effects, response biases). Assessments included: Cohen’s effect size estimates of item-level sensitivity and scale-level external responsiveness; item-to-total correlations; Cronbach’s alpha for internal consistency reliability; Spearman correlations against reference measures for construct validity; known-groups analyses for discriminating ability; t-tests of within-group differences between baseline and postbaseline visits for internal responsiveness; multiple anchor-based approaches to estimate minimum clinically important change (MCIC). **Results:** No significant item- or scale-level distribution anomalies were noted. Individual items appeared sensitive to treatment group differences. All item-to-total correlations were positive and most were significant ( $p < 0.01$ ).

Internal consistency (Cronbach's alpha) was within the optimal range (0.81). In general, correlations between Y-BOCS-BE scores and other measures were significant and in the direction expected, providing support for convergent and discriminate validity; change score correlations were of greater magnitude than baseline score correlations. Medium change score correlations (0.4 to 0.7) were seen between Y-BOCS-BE score and number of binge days (0.38), CGI-S (0.57), TFEQ disinhibition and hunger subscales (0.57 and 0.52, respectively), BIS-11 (0.58), and CGI-I (0.58). There were no significant correlations between change scores for the Y-BOCS-BE and the MADRS or HAM-A. MCIC estimates ranged from -4 to -17. Discussion: This research provides supportive evidence for use of the YBOCS-BE as a measure of treatment benefit in clinical studies involving BED, with data indicating high internal consistency reliability and strong support for construct validity. In moderate-to-severe BED (based on binge frequency), the Y-BOCS-BE showed good ability to discriminate between known groups and was responsive to changes over time and to intervention. In summary, the Y-BOCS-BE was found to be a reliable and valid measure of an important but unique concept in BED-related clinical studies. Study limitations include using protocol-defined BED severity level and the exclusion of psychiatric comorbidities. Learning Objectives: Understand the methods and results evaluating key Y-BOCS-BE measurement properties 1. Item-level distributional examination and between-group sensitivity 2. Internal consistency reliability 3. Convergent and discriminant validity 4. Responsiveness 5. Threshold estimates of clinically meaningful change.

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## **ACQUIRED BINGE-EATING BEHAVIOUR PRODUCES ALTERATIONS IN DOPAMINERGIC NEUROCHEMISTRY IN THE BRAINS OF RATS**

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Background Binge-eating disorder (BED) is a common psychiatric condition, affecting ~2% of the adult population. It presents as the compulsive, excessive consumption of highly palatable foods. BED is often associated with obesity, but a significant proportion of sufferers are of normal weight. We have developed a rodent model of BED in which rats are given irregular, limited access to chocolate. These rats develop robust, intermittent, hyperphagia of this palatable food. They show concomitant reductions in consumption of normal chow and so maintain a normal bodyweight (1). This rodent model mirrors human BED without associated obesity. Recent evidence has linked eating disorders with CNS dopaminergic dysregulation (2,3). . Methods Forty-five adult female Wistar rats were housed individually on reversed-phase lighting with free access to standard diet and water. Ground milk chocolate was offered to each rat for 2h periods at irregular intervals over a 28-day period during which time they developed binge eating. Control rats were treated identically except that an empty glass jar was placed in their cages during the binge sessions. Rats were killed 1 hr after the final binge session. Dopamine (DA) and its metabolites (dihydroxyphenylacetic acid [DOPAC], homovanillic acid [HVA] and 3-methoxytyramine [3 MT]) were measured in striatum (STR), prefrontal cortex (PFC) and hypothalamus (HPT) by HPLC-ECD. D1 and D2 receptors were quantified by saturation binding analysis in STR membranes using [3H]SCH23390 and [3H]raclopride, respectively. Results Acquired binge-eating behaviour did not alter the concentration of dopamine or its metabolites in STR, PFC or HPT of the rats. Compared with controls, DA turnover (DA:DOPAC ratio) was significantly increased by 18% ( $p<0.05$ ) in HPT in binge eating rats, but it was not altered in STR or PFC. STR D1 receptors were significantly reduced by 27% in binge eating rats ( $B_{max}$ [fmol/mg tissue]: Binge-eating =  $10.9\pm1.0$ ; Control =  $15.0\pm1.4$ ;  $p<0.025$ ), but D2

receptors were unaltered ( $B_{max}$ [fmol/mg tissue]: Binge-eating =  $12.2 \pm 0.6$ ; Control =  $12.3 \pm 0.6$ ). The affinity ( $K_d$ ) values of D1 and D2 receptors for [3H]SCH23390 and [3H]raclopride were unchanged in the binge-eating rats. Conclusions Binge-eating behaviour decreased the number of STR D1 receptors without altering the number of D2 receptors, the size of the dopamine neuronal pool or the rate of dopamine turnover. These results indicate that binge-eating is associated with decreased dopaminergic signalling via D1 receptors and possibly an imbalance between striatal D1/D2 signalling. Dopaminergic neurotransmission was not altered in the PFC. Increased DA turnover in HPT suggests that in this region, which is an important regulator of food intake, dopaminergic signalling is also dysregulated in binge-eating.

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#### Learning Objectives:

- Dopamine neurochemistry in various brain regions.
- D1 and D2 receptors in the striatum.

**Source of Funding:** Shire

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### DEFINITIVE VERIFICATION AND MONITORING OF ORAL MEDICATION ADHERENCE USING BREATH ANALYSIS

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Background: Poor medication adherence is a major contributor to variability in drug response and adversely impacts clinical research, drug development, and clinical outcomes. A breath-based technology has been developed to document ingestion of a FDA-designated food additive (GRAS compound), as an adherence marker (AM), to reliably generate characteristic breath markers detected by a hand-held miniature gas chromatograph (mGC) designed to collect and analyze breath samples. Study objectives: The study objectives are to define the optimal operating configuration of the SMART® System, and determine the optimal AM (2-butanol) formulation and the breath kinetics of 2-butanone. Study design: The study design is a prospective, randomized, triple-blind, crossover study in 50 study participants using four 2-butanol (AM) formulations and six breath sampling intervals over four study visits. Study results: The outcome measure was the change from baseline in 2-butanone concentration recorded at each time point during the sampling interval. The SMART® System performance was favorable and demonstrated that 2-butanone breath PK and its inter-individual variability across 50 subjects is sufficiently low to permit 2-butanone to be reliably detected in the breath. For the lead AM formulation, 100% of responders had  $\Delta$ 2-Butanone levels detectable at 60 minutes and greater than 98% of subjects gave an overall positive response. Adherence accuracies exceeding 95% can be achieved when a 20-60 min breath marker detection window is employed. Conclusion: The SMART® System was found to be patient friendly and its performance was also favorable across a wide range of subject factors, including age, gender,

race, body mass index (BMI), disease conditions, and time of food ingestion. The SMART® System offers definitive and noninvasive monitoring of medication adherence in near real time, utilizing exhaled breath to confirm that medication has been taken by study participants as directed. The handheld SMART® miniature gas chromatograph device detects and measures exhaled drug ingestion markers that are generated from GRAS food additives to verify medication adherence.

### **Learning Objectives:**

- What is this breath-based adherence technology?
- What will the breath-based adherence technology provide?

**Source of Funding:** Xmal SMART, Inc.

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## **PREDICTORS OF PHARMACOLOGICAL TREATMENT RESPONSE IN GROOMING DISORDERS**

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**Purpose:** Grooming disorders, including trichotillomania (TTM) and excoriation (skin picking) disorder (SPD), are often disabling psychiatric conditions that follow a chronic course. Despite their frequent occurrence in both general and psychiatric settings, treatments are extremely limited and no FDA-approved medications exist for either condition. Limited knowledge exists regarding effective treatments or predictors of treatment response for those who do experience benefits through pharmacotherapy. **Aims:** This study sought to examine predictors of treatment response in a sample of clinical trial patients with TTM or SPD by exploring aspects of demographics, clinical characteristics and neurocognition. By examining this issue, clinicians may be better able to triage patients with specific characteristics to appropriate pharmacological intervention. **Methods:** Subjects enrolled in pharmacotherapy trials conducted from 2004-2014 at two large Midwestern US medical centers who 1) completed at least one post-baseline visit after receiving study medication and 2) had undergone pre-treatment neurocognitive testing examining motor inhibition and cognitive flexibility, were included in this analysis. A total of five medication studies were included: lamotrigine, naltrexone, n-acetylcysteine, and dronabinol. Given relatively small numbers of patients and substantial clinical and phenomenological overlap between TTM and SPD, we grouped all patients into a category of “grooming disorders”. Response to treatment was defined as an endpoint Yale-Brown Obsessive Compulsive Scale modified for Neurotic Excoriation score of  $\leq 10$  (for SPD subjects) or a Massachusetts General Hospital Hair Pulling Scale score of  $\leq 7$  (for TTM subjects). These scores denote ‘remission’ of symptoms. **Results:** A total of 114 patients (n=57 with TTM; n=57 with SPD) (mean age:  $33.1 \pm 11.4$ ; 89.5% female) were included in the analysis. Patients classified as responders (n=28; 24.5%) had a mean decrease of 70.2% from baseline severity to endpoint compared to 25.4% in the non-responder (n=86) group. Older age, being married, and having lower levels of baseline severity predicted treatment response. There were no significant cognitive profiles that were predictive of response to pharmacotherapeutic treatment. **Importance:** Grooming disorders are poorly understood and undertreated psychiatric conditions. Pharmacotherapy may be particularly useful for a subset of individuals with grooming disorders. Clinicians should be aware that alternative treatments, such as habit reversal therapy, or adjunctive treatment may be necessary for grooming disorders patients presenting with more clinically severe symptoms. Further



research into treatments is sorely needed as less than one in four patients in this analysis were classified as in remission.

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#### **Learning Objectives:**

- Pharmacotherapy may be particularly useful for individuals with a grooming disorder who are older, married, and have a moderate level of severity.
- Patients presenting with more severe symptoms may require pharmacotherapy adjunctive with a psychotherapeutic approach.

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### **WEB-BASED CURRICULUMS FOR TEACHING PSYCHOPHARMACOLOGY: REVISION OF THE RESIDENT AND THE MEDICAL STUDENT CURRICULUMS**

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Introduction: The ASCP Psychopharmacology Committee has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to psychiatric residents and medical students. Several ‘consumer’ surveys of the psychopharmacology curricula have highlighted the need to have it available online. We present here the 7th edition of the resident curriculum and the 2nd edition for medical students – now available online. Methods: 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 both curriculums within the last 2 years. Results: We describe here the process of revising, updating, and moving to a web-based curriculum. We will present the content for the two curriculums. Based on the follow-up of the Medical Student Curriculum, we have revised every lecture. Discussion: For teaching medical students, 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. For residents, the curriculum is now in its 7th editions and has 88 lectures and over 4,000 slides. Having the curriculum web-based has improved availability although some programs globally still want a hard copy version.

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### **THE EFFECTS OF SOCIAL SUPPORT ON SUICIDALITY IN AN ADULT INPATIENT PSYCHIATRIC POPULATION AS ASSESSED BY THE C-SSRS AND S-STS**

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**Introduction:** Recent literature has emphasized identifying factors that affect the risk for suicidal ideation and behavior. Studies of the general population have demonstrated that social support may protect against suicidality (1). The current study examines this concept by using two standardized suicide assessment instruments in a psychiatric inpatient sample. **Method:** Data were collected and analyzed as part of an original study comparing suicide assessment instruments in adult psychiatric inpatients (n = 199; 43.2% male, 56.8% female). Past month suicidal ideation and behavior were evaluated using the Columbia Suicide Severity Rating Scale (C-SSRS) (2) and the Sheehan Suicidality Tracking Scale (3). A Risk Assessment Measure (RAM) assessed several dimensions of social support. **Analysis:** As part of a secondary analysis, chi-square tests tested for relationships between suicidality and having a supportive family, having one or more good friends, having recently lost a very close friend or family member, and feeling lonely. Phi was calculated to determine the magnitude of relationships. **Results:** 71.4% (n = 142) of patients reported having a supportive family and 84.4% (n = 168) reported having one or more good friends. 51.3% (n = 102) lost a close friend or family member in the past year and 77.9% (n = 155) frequently felt lonely. Loneliness was less common among those with a supportive family ( $\phi = 0.23$ ) but was unrelated to having good friends or to a recent loss. Those with a supportive family had less suicidal ideation on the C-SSRS and S-STS than those without; phis ranged from 0.16 to 0.28. Having one or more good friends did not have a statistically significant effect on suicidality. Those who had not lost someone close in the past year were less likely to have made an aborted suicide attempt according to the C-SSRS ( $\phi = 0.16$ ). Those who did not feel lonely were less likely to have C-SSRS and S-STS suicidal ideation (phis from 0.19 to 0.28) and C-SSRS suicidal behavior ( $\phi = 0.17$ ). **Discussion:** The data suggest that social support definitively protects against suicidal ideation, but may only slightly protect against suicidal behavior. To the best of our knowledge, this study is the first to utilize two standardized suicide assessment instruments to assess social support as a protective factor against suicidality. Clinicians should inquire about their patients' social support and should address any deficits there to reduce the risk for suicidality.

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### **Learning Objectives:**

- Examine relationship between suicidality and social support in an inpatient psychiatric setting.
- Contribute to literature on protective factors for suicidality.

*Jeffrey Mattes*

*Psychopharmacology Research Association of Psychopharmacology Research Association of Princeton*

Many ASCP meeting attendees teach psychopharmacology. In order for clinical treatment to be optimized, research-oriented psychiatrists must help clinicians to distinguish between promotion and true differences between medications. The more accurate doctors are in making this distinction, the more motivated drug companies will be to develop truly better medications (a difficult task), rather than vigorously promoting “me too” drugs. In 2011, I presented a talk at the NCDEU with the same title as this poster. The talk coincides with attempts by others, e.g., the Pew Prescription Project, and Prescription Policy Choices, who attempt to counteract the effect of drug company promotion (partly to reduce drug costs). This poster will present slides similar to those I presented at NCDEU in 2011, but more suitable to a course in psychopharmacology. The slides are available to anyone interested (no charge). A representative selection of these slides will be presented on the poster, and the others will be available on a laptop computer at the poster site. The slides will present topics such as the following: 1. Implying Rather Than Proving Superiority: e.g., rather than conducting studies to prove that SNRI’s are better than another SSRI for patients who fail an SSRI, companies preferred to imply in promotional material that the norepinephrine effect was clinically helpful. 2. The New Indications Stratagem: e.g., getting FDA approval for an SSRI for Panic Disorder, and implying that the drug is then better for Panic Disorder than other SSRI’s (or tricyclics) which were not specifically FDA approved for Panic Disorder. 3. Ignoring the Forest, Focusing on a Favorite Tree: e.g., the one most evident result of the CATIE study was that more patients should be on clozapine. However, drug companies focused on other issues, to benefit their particular atypical. 4. Comparing Newer Drugs with Older Drugs, but Using the Older Drugs Less than Optimally: e.g., comparing the speed of onset of Depakote vs. Lithium for mania, or comparing atypical neuroleptics to an unnecessarily high dose of haloperidol. 5. Statistical Obfuscation: e.g., using very large samples to obtain a statistically significant effect which is not clinically significant (e.g., Alzheimer’s drugs). 6. Promotion Masquerading as “Evidence-Based Medicine”: e.g., a paper which concluded that there is little evidence that trazodone works for insomnia was funded by a company promoting a hypnotic. Similarly, articles promoting Abilify to augment antidepressants have made the point that many more patients have been studied with Abilify as an augmenting agent than with, for example, lithium. But this is because the company making Abilify spent the money needed for studies; it doesn’t indicate that Abilify is better than lithium. These and other issues, in slide format, will be presented in the poster. Some may consider this topic not appropriate for an ASCP meeting. Others may see it as a “breath of fresh air”, in a room dominated by posters funded by drug companies. Hopefully a majority will see this as a small attempt to “balance the scales”, helping physicians to obtain a more accurate assessment of the value of new medications.

### **Learning Objectives:**

- To understand: If the true value of new medications are known (without marketing “spin”), drug companies can only profit by developing truly better medications.
- To understand some of the ways that drug company promotion can imply that a new drug is better than an older drug, when it really isn’t.

## **METABOTROPIC GLUTAMATE RECEPTOR 7 (GRM7) PHARMACOGENETICS IN FIRST EPISODE PSYCHOSIS**

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Background: Genes involved in glutamate transmission have recently been associated with antipsychotic treatment response, as well as susceptibility to schizophrenia and cognitive performance. Whether these findings are disease specific or may be more broadly related to a psychosis phenotype has not been determined. We examined genetic markers across a panel of glutamate-related genes to determine whether there are pharmacogenomic relationships with symptom response to antipsychotics in first-episode psychosis patients. Methods: Eighty-eight patients experiencing their first psychotic episode (schizophrenia n=69, bipolar disorder with psychotic features n=11, major depressive disorder with psychotic features n=8) and who were currently untreated with no or minimal prior antipsychotic exposure were enrolled into a pharmacogenomic study of treatment response. Symptoms were evaluated before and after six weeks of antipsychotic treatment using the Brief Psychiatric Rating Scale (BPRS). Risperidone was the preferred antipsychotic (n=70) with others chosen as secondary options. Genotyping was performed using the Affymetrix SNP 6.0 Array. Genetic data from the array was analyzed in a hypothesis driven approach whereby 3,072 common single-nucleotide polymorphism (SNPs) in 58 genes involved in glutamate transmission were examined. Permutation analysis (n=10,000) was used to generate point-wise and experiment wise significance values to minimize type-I error and adjust for multiple comparisons. Models were also adjusted for clinical factors such as baseline symptoms, ancestry, and chlorpromazine equivalent antipsychotic dose. Results: Eight of the 20 SNPs most strongly associated with symptom response on the BPRS, including the top two variants, were in GRM7 (all p<0.003). These findings were primarily driven by changes in positive symptoms. Associated GRM7 variants were predominantly localized to an 18 kb region of GRM7 in intron 11 near the 5' end of the gene. Findings related to rs2069062 represented BPRS Total change scores of 12.0 (CC n=59), 5.6 (CG n=25), and 1.8 (GG n=4) (p<0.001 adjusted for race, baseline symptoms, and chlorpromazine equivalent dose). These findings represent clinically-meaningful effect sizes, however did not retain statistical significance after an experiment-wide adjustment for multiple testing was applied. These findings were similar when examining the subgroup of schizophrenia patients only. Conclusions: GRM7 encodes the presynaptic mGluR7 group-III metabotropic glutamate receptor-7. We identified that the variant allele of the intronic rs2069062 SNP was associated with numerically worse clinical response in an additive fashion. Recent evidence suggests that agonizing mGluR7 results in decreased NMDA receptor activity. While the exact function of this SNP requires further exploration, our results are consistent with the hypothesis that altered mGluR7 function may represent a mechanism for treatment resistance or persistent symptoms during the course of early treatment. Our findings represent potentially clinically meaningful effects that warrant validation in additional study samples.

### **Learning Objectives:**

- Study antipsychotic response in first episode psychosis patients.
- Examine pharmacogenetic relationships between glutamate gene variants and clinical response in first episode psychosis.

**Source of Funding:** This study was supported by National Institute of Health (NIH) grants MH083888, MH062134, MH083126, MH45156, MH63480, RR024153, CTSA Grant UL1TR000050 and NIH/NCRR/GCRC Grant RR00056, American College of Clinical Pharmacy, Vahlteich Foundation, Janssen Pharmaceuticals, and the Alexander von Humboldt Foundation.

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## **MEDICAL INFORMATICS IN PSYCHIATRIC PRACTICE: CURRENT STATUS AND UNMET NEEDS**

*Farifteh Duffy<sup>1</sup>, Laura Fochtmann<sup>2</sup>, Robert M. Plovnick<sup>3</sup>, Diana E. Clarke<sup>4</sup>, Eve K. Mościcki<sup>4</sup>, William Narrow<sup>4</sup>*

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**Background:** A major challenge for psychiatrists is the need to maintain expertise in the face of an ever-expanding evidence base and an ever-shrinking amount of time to update their clinical knowledge and incorporate it into their practices. Little is known about the extent to which practicing psychiatrists use paper-based and computer-based information resources, their common sources for information, and what they consider as gaps in information resources. **Study Aims:** The study aims are to identify psychiatrists' sources for gathering clinical information and assess current unmet information needs, in order to inform the development of user-friendly clinical information resources and practice guidelines. **Design:** This cross-sectional, observational study was fielded in 2011, using Web- and paper-based survey methods. **Population Studied:** 1,000 psychiatrists were randomly selected from the AMA Physician Masterfile. After excluding ineligible individuals, 151 responded (18.4%). **Findings:** Initial findings indicate that 69% of psychiatrists regularly used computers and other electronic platforms for clinical purposes and professional education. The most frequent uses were documenting encounters (55%), e-prescribing (39%), reading lab results (32%), obtaining general clinical information (31%), and communication with other clinicians (26%). In a typical work week, psychiatrists reported that nearly 15 % (range = 0% to 90%) of their clinical encounters prompted clinical question(s) requiring additional information gathering and resources. The most commonly used resources included internet search (78%), professional journals (67%), colleagues (64%), other drug information resources such as MicorMedex (58%), Wikipedia (45%) and package inserts (43%). When asked about current unmet needs, respondents most commonly cited the necessity for a centralized/consolidated, well-vetted resource for currently available medications, with transparent research data that includes information on drug-drug interaction, side effects, cost, and pharmacotherapies for comorbid conditions. **Conclusion:** Practicing psychiatrists employ computers and other electronic platforms for a variety of clinical and educational purposes. They use a variety of information resources to deal with questions that arise during clinical encounters. A number of respondents identified a centralized resource of pertinent, up-to-date, evidence-based information on psychopharmacotherapy as a critical requisite for the field.

### **Learning Objectives:**

- The overall objective is to inform the development of user-friendly clinical information resources and practice guidelines by identifying.
- Psychiatrists' sources for gathering clinical information.
- Their current unmet information needs.

**Source of Funding:** This study was supported by the National Library of Medicine (G08 LM010710), "Using Medical Informatics Principles to Enhance Development and Dissemination of Clinical Practice Guidelines on Major Depressive Disorder."

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## **ALL-CAUSE DISCONTINUATION AND SAFETY OF ARIPIPRAZOLE ONCE-MONTHLY FOR THE TREATMENT OF SCHIZOPHRENIA: A POOLED ANALYSIS OF TWO DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS**

W. Wolfgang Fleischhacker<sup>1</sup>, Raymond Sanchez<sup>2</sup>, Lan-Feng Tsai<sup>2</sup>, Timothy Peters-Strickland<sup>2</sup>, Ross A. Baker<sup>2</sup>, Anna Eramo<sup>3</sup>, John Kane<sup>4</sup>

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**Purpose:** Switching medications is a common feature of psychiatric practice. When a change in antipsychotic medication is considered, the potential benefits and risks of switching must be evaluated. The objective of this pooled analysis was to evaluate the initial (3 months) all-cause discontinuation and safety of aripiprazole once-monthly 400 mg (AOM-400 mg), an extended release injectable suspension of aripiprazole and the first dopamine partial agonist available as a long-acting injectable formulation, stratified by previous treatment. **Methods:** These were 2 double-blind, placebo- or active-controlled studies (NCT00705783 & NCT00706654) assessing the efficacy and safety of AOM-400 mg. Detailed study designs were reported previously.<sup>1,2</sup> This analysis was conducted in the pooled population in the first 3 months after initiating AOM-400 mg in patients who received  $\geq 1$  dose of AOM-400 mg. Outcome measures are reported for groups stratified by prior treatment. **Results:** In total, 841 patients received  $\geq 1$  dose of AOM-400 mg: 191 who entered on oral aripiprazole, 581 who converted from another antipsychotic, and 69 who had no prior antipsychotic treatment. In these groups of patients, during the first 3 months of treatment, rates of discontinuations due to all-causes (not including those who discontinued due to the sponsor stopping the NCT00705783 study early after pre-specified efficacy parameters were met) were 13.2% (n=111/841), 12.0% (23/191), 13.1% (76/581), and 17.4% (12/69), respectively, and rates of discontinuations due to adverse events (AEs) were 2.5% (21/841), 1.6% (3/191), 2.4% (14/581), and 5.8% (4/69), respectively. In the first 3 months, insomnia was the most common AE, with rates of 8.4% (71/841), 3.1% (6/191), 9.8% (57/581), and 11.6% (8/69) in the overall patient population, patients who entered on oral aripiprazole, patients converted from another antipsychotic, and patients with no prior antipsychotic treatment, respectively; rates of akathisia were 7.0% (59/841), 7.9% (15/191), 6.7% (39/581), and 7.2% (5/69), respectively. **Conclusion:** AOM-400 mg appeared equally safe and effective (as measured by all-cause discontinuation) in the first 3 months after initiation, regardless of treatment prior to entering trials.

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### **Learning Objectives:**

- Characterize treatment persistence with aripiprazole once-monthly during the first 12 weeks of treatment in patients with schizophrenia.
- Characterize the safety of aripiprazole once-monthly during the first 12 weeks of treatment in patients with schizophrenia.

**Source of Funding:** Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S

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### **SUBJECT RECRUITMENT STRATEGIES: A NEW CROSS-FUNCTIONAL TEAM APPROACH**

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Background: Rapid clinical trial recruitment is critical for reducing drug development costs and maximizing product value. Recruitment can be particularly difficult in innovative trials. The Paliperidone Research In Demonstrating Effectiveness (PRIDE) study (NCT01157351) is a 15-month, randomized, open-label, multicenter, US study comparing paliperidone palmitate with oral antipsychotics in a community sample of schizophrenia subjects with a history of incarceration. Primary endpoint was improvement in time to treatment failure relative to oral antipsychotics. Despite the reported abundance of such persons in the schizophrenia population, trial initiation was marked by recruitment difficulties, with few investigators able to find eligible subjects. We describe an innovative investigator-community-sponsor relationship that led to a successful patient recruitment and study site support strategy. Methods: Initial recruitment strategies included selecting study sites that identified themselves as treating individuals with schizophrenia who have had contact with the criminal justice system (CJS). Using standard recruitment practices, investigators were unable to identify and recruit patients per their original recruitment plan. Key to turning this challenge into success was development and implementation of a strategic plan for each site that included identifying and networking with community-based mental health system personnel. Synergistic partnership of medical science liaisons (MSLs) and site managers in leveraging each other's core competencies supported the patient recruitment plan at each site. The plan that was developed focused on study sites collaborating with community-based services, supportive housing, diversion programs, law enforcement, and CJSs. Results: The innovative recruitment strategy developed for PRIDE was successful in meeting the trial's enrollment goals. Recruitment increased by approximately 50% at sites where the study site support strategies were implemented. Conclusions: The success of PRIDE in enrolling a representative population of patients with schizophrenia linked to the CJS

was rooted in pretrial preparation and engagement of MSLs and internal operations partners within the organization, as well as site staff and community members, in supporting this population. Lessons learned during planning and conduct of the PRIDE study will provide a foundation for design and development of future trials and improved physician/patient outcomes.

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- Greenberg G, Rosenheck RA, Erickson SK, Desai RA, Stefanovics EA, Swartz M, Keefe RS, McEvoy J, Stroup TS; CATIE Investigators. Criminal justice system involvement among people with schizophrenia. *Community Ment Health J* 2011; 47(6):727-736

#### **Learning Objectives:**

- To educate participants on the issue of clinical trial recruitment in a schizophrenia population.
- To educate participants on an innovative recruitment strategy for a clinical trial that included a community sample of schizophrenia subjects with a history of incarceration.

**Source of Funding:** Support: Janssen Scientific Affairs, LLC.

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#### **ACCELERATED AGING IN SEVERE MENTAL ILLNESS USING LEVELS OF ADVANCED GLYCATED ENDPRODUCTS AS INDICATOR. RESEARCH FINDINGS AND CLINICAL CONSEQUENCES**

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Objectives: Reduced life expectancy in schizophrenia of 12-32 years, and an odds ratio around 2 for cardiovascular (CV) mortality have been consistent findings. Thus, evidence exists for accelerated ageing occurring in schizophrenia. Accumulation of Advanced Glycated Endproducts (AGE's), non-invasively measured by skin auto fluorescence (AF), shows a steady increase during lifespan from (< 10 years up to > 80 years), has been shown to be a predictor of CV mortality in diabetes and chronic kidney disease, and is considered as a marker of aging. Our aim was to compare skin-AF levels in schizophrenia and related psychiatric disorders, with those in the general population and to identify possible explanatory variables. Methods: skin-AF/AGE-levels in normoglycemic outpatients with severe mental illness over a wide calendar age (20-70 years) were assessed and compared with normative data of the general population. Possible predictive variables were obtained partly by interviewing patients according to an interview format and partly by retrieving data from the electronic patient files. Results: The study population consisted of 285 patients with severe mental illness (SMI) .of whom 202 were diagnosed with schizophrenia or other psychotic disorders. The AF-values were found to be markedly and significantly increased in all 5 age cohorts, both in the total sample as well as in the schizophrenia subgroup. The calendar age of the patients explained 27% of the AF variance, compared to 60% in the general population. Correction for smoking, duration of illness or duration of antipsychotic medication did not change the results. Conclusion: AF-measurement of AGE's shows considerably elevated levels in SMI without specificity for schizophrenia,



especially in younger calendar age decades. Skin AF may be of help in estimating the biological age, and so may contribute to an early and more appropriate assessment and treatment of cardiovascular risk factors in this high-risk population.

### **Learning Objectives:**

- This study confirms the concept of accelerated ageing in patients with severe mental illness, both in the population with diagnosed schizophrenia as in the population with other psychiatric disorders.
- Accelerated aging can easily and non-invasively be assessed with skin auto-fluorescence measurement of skin advanced glycated end-products (AGE's).

**Source of Funding:** Unrestricted grant from FondsNutsOhra, Netherlands

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### **A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY OF LURASIDONE FOR THE MAINTENANCE OF EFFICACY IN PATIENTS WITH SCHIZOPHRENIA**

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*<sup>1</sup>University of Florida College of Medicine, <sup>2</sup>Sunovion Pharmaceuticals, Inc.*

Background and Objective: Relapse in schizophrenia has been associated with a progressive decline in treatment response and worsening of the disease course.<sup>1</sup> Long-term treatment is necessary to control symptoms and minimize the occurrence of psychotic relapse.<sup>2</sup> The objective of this study (ClinicalTrials.gov identifier: NCT01435928) was to evaluate the efficacy of lurasidone as maintenance treatment for schizophrenia. Methods: Adult patients experiencing an acute exacerbation of schizophrenia were enrolled in the 12- to 24-week open-label stabilization phase of the trial, during which they were treated with lurasidone (40-80 mg/d, flexibly dosed). Patients who maintained clinical stability for  $\geq 12$  weeks during the open-label phase were randomized to placebo or lurasidone (40-80 mg/d, flexibly dosed) in the 28-week, double-blind phase. The primary efficacy endpoint was time to relapse, with the nominal p value for statistical significance adjusted from 0.05 to 0.042 due to pre-specified un-blinded interim analyses. Secondary efficacy measures included change from double-blind baseline in Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression–Severity (CGI-S) scores. Safety assessments included treatment-emergent adverse events, discontinuations due to adverse events (AEs), and laboratory measures. Results: Of 676 enrolled patients, 285 met protocol-specified stabilization criteria and were randomized to lurasidone (N=144) or placebo (N=141). Relapse occurred in a greater proportion of patients receiving placebo (41.1%) than lurasidone (29.9%). Time to relapse was significantly longer for lurasidone compared with placebo (log-rank test,  $p=0.039$ ). Lurasidone was associated with a 33.7% reduction in risk of relapse versus placebo (Cox model hazard ratio [95% confidence interval], 0.663 [0.447, 0.983];  $p=0.041$ ). Patients receiving placebo demonstrated significantly greater worsening on PANSS and CGI-S scores compared with lurasidone-treated patients (PANSS least-squares mean change, +12.4 vs +8.3,  $p=0.029$ ; CGI-S mean change, +0.7 vs +0.4,  $p=0.015$ ; analysis of covariance with the last observation carried forward). The percentage of patients reporting any AE was similar in the lurasidone (53.5%) and placebo (54.6%) groups. The most commonly reported AEs (with incidence  $\geq 3\%$  in lurasidone-treated patients and  $>$  placebo) during the double-blind phase were anxiety (4.2% vs 2.8%), back pain (4.2% vs 2.1%), and weight increased (3.5% vs. 2.8%). The

discontinuation rate due to AEs was 13.9% for lurasidone and 15.6% for placebo. Minimal changes in weight, prolactin, lipid, and glucose parameters were observed. Conclusion: This placebo-controlled, randomized withdrawal study demonstrated the efficacy of lurasidone for the maintenance treatment of patients with schizophrenia. Lurasidone was generally well tolerated, with minimal effects on weight and other metabolic parameters.

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- Emsley R et al, Schizophr Res 2013; 148:117-121
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#### Learning Objectives:

- Discuss the effectiveness of lurasidone for maintenance treatment of patients with schizophrenia.
- Describe the long-term safety and tolerability profile of lurasidone.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals, Inc.

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#### CATEGORICAL IMPROVEMENTS IN DISEASE SEVERITY IN SCHIZOPHRENIA PATIENTS TREATED WITH CARIPRAZINE

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<sup>1</sup>Forest Research Institute, <sup>2</sup>Gedeon Richter Plc, <sup>3</sup>Apostle Clinical Trials Inc.

Background: Schizophrenia is a severe mental illness characterized by a diverse set of symptoms that can lead to patient distress, functional impairment, and poor quality of life. Reducing the overall severity of illness and improving global functioning is an important treatment goal. While symptom specific scales, such as the Positive and Negative Syndrome Scale (PANSS), evaluate symptom severity more broad assessments like the Clinical Global Impression-Severity (CGI-S) scale allows for evaluation of overall disease severity including symptom intensity, patient functioning, and quality of life. Cariprazine is an orally active and potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. Cariprazine was effective and generally well tolerated in 3 phase II/III studies in patients with schizophrenia. In this pooled analysis, the effect of cariprazine on overall disease severity was evaluated by measuring clinically relevant shifts in CGI-S scores. Methods: Data were pooled from 3 positive, Phase II/III, double-blind, placebo-controlled trials in patients with acute exacerbation of schizophrenia (NCT00694707, NCT01104766, NCT01104779). All cariprazine dose groups were combined for analyses (cariprazine dose range, 1.5 to 9 mg/day). The secondary efficacy parameter in all 3 studies was change from baseline in the CGI-S. In this post hoc analysis, improvements in global disease severity at Week 6 were assessed by analyzing the proportion of patients shifting from a baseline CGI-S score of  $\geq 6$  (severely ill or worse) to endpoint score of  $\leq 3$  (mildly ill or better). Additional analyses included CGI-S score shifts from  $\geq 5$  (markedly ill or worse) to  $\leq 2$  (borderline ill/normal). Data were analyzed using a logistic regression model and odds ratios (OR) were determined. Results: In the individual studies, all cariprazine dose groups showed superiority to placebo ( $P < .05$ ) on mean change from baseline to Week 6 in CGI-S scores. Least square mean differences (LSMD) ranged from -0.3 to -0.6. The pooled population comprised 161 patients (placebo,  $n=50$ ; cariprazine,  $n=111$ ) that were classified as severely or extremely ill and 1033 patients (placebo,  $n=311$ ; cariprazine,  $n=722$ ) that were at least markedly ill. A

significantly greater proportion of severely ill patients at baseline improved to mildly ill or better in the cariprazine group compared with placebo (42% vs 18%; OR=3.43 [95% CI: 1.5, 7.9]; P=.004). In patients who were markedly ill or worse at baseline, 7% of cariprazine vs 3% of placebo patients improved to borderline ill/normal at Week 6 (OR=2.33 [95% CI: 1.1, 4.8]; P=.022). Conclusions: Cariprazine treatment compared with placebo resulted in a significantly greater proportion of patients achieving clinically relevant improvements in global disease severity as measured by CGI-S category shifts.

### Learning Objectives:

- At the conclusion of this session, the participant should be able to evaluate the efficacy of cariprazine treatment on overall disease severity in patients with schizophrenia.
- At the conclusion of this session, the participant should be able to compare the treatment effects of cariprazine in patients with different levels of global disease severity.

**Source of Funding:** Supported by funding from Forest Laboratories, Inc. and Gedeon Richter Plc

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### EFFICACY AND SAFETY OF ARIPIPRAZOLE ONCE-MONTHLY IN OBESE AND NON-OBESE PATIENTS WITH SCHIZOPHRENIA: A POST HOC ANALYSIS

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<sup>3</sup>Otsuka Pharmaceutical Europe, Ltd, <sup>4</sup>Otsuka Pharmaceutical Development & Commercialization, Inc.

**Purpose:** To evaluate the efficacy and safety of aripiprazole once-monthly 400 mg (AOM-400 mg), an extended-release injectable suspension of aripiprazole, in obese (body mass index [BMI],  $\geq 30$  kg/m<sup>2</sup>) and non-obese (BMI,  $< 30$  kg/m<sup>2</sup>) patients with schizophrenia. **Methods:** Data from a 38-week, double-blind, active-controlled noninferiority study (NCT00706654)<sup>1</sup> with randomization (2:2:1) to AOM-400 mg, oral aripiprazole (10–30 mg/d), or aripiprazole once-monthly 50 mg (AOM-50 mg) assessing the efficacy and safety of aripiprazole in patients requiring chronic antipsychotic treatment were used for this post hoc analysis. We report the overall relapse rates in the 38-week randomized phase. Comparisons of overall relapse rates were analyzed using the chi-square test. **Results:** 662 patients were randomized to AOM-400 mg (n=265), oral aripiprazole (n=266), or AOM-50 mg (n=131). Of these, the following were obese: AOM-400 mg, n=95 (36%); oral aripiprazole, n=95 (36%); and AOM-50 mg, n=43 (33%). In the obese patients, the overall relapse rate was significantly ( $P=0.0012$ ) lower with AOM-400 mg (7.4%) than with AOM-50 mg (27.9%). The difference between AOM-400 mg and oral aripiprazole (8.4%) was not significant. In the non-obese patients, the overall relapse rate was significantly ( $P=0.0153$ ) lower with AOM-400 mg (8.8%) than with AOM-50 mg (19.3%). The difference between AOM-400 mg and oral aripiprazole (7.6%) was not significant. For patients treated with AOM-400 mg, the most common treatment-emergent adverse events (AEs) ( $>10\%$  in any group) for obese vs non-obese patients were insomnia (12.6% vs 11.2%, respectively), headache (12.6% vs 8.2%), injection site pain (11.6% vs 5.3%), akathisia (10.5% vs 10.6%), and upper respiratory tract infection (10.5% vs  $<5\%$ ). Increased weight was reported as an AE in 10.5% of obese and 8.2% of non-obese patients. In patients treated with 400 mg, the incidence of shifts from non-obese at baseline to obese during the randomized phase was 7.6% (n=13/170);

the incidence of shifts from obese to non-obese was 17.9% (17/95). **Conclusions:** The efficacy and tolerability of AOM-400 mg were similar in obese and non-obese subgroups. **References** 1. Fleischhacker WW, Sanchez R, Perry PP, Jin N, Peters-Strickland T, Johnson BR, et al. Aripiprazole once-monthly for treatment of schizophrenia: a double-blind, randomized, non-inferiority study. Submitted 2. Weber NS, Cowan DN, Millikan AM, Niebuhr DW. Psychiatric and general medical conditions comorbid with schizophrenia in the National Hospital Discharge Survey. *Psychiatry Serv.* 2009;60(8):1059-1067

### **Learning Objectives:**

- Characterize the efficacy of aripiprazole once-monthly in obese versus non-obese patients with schizophrenia.
- Compare the frequency of common adverse events with aripiprazole once-monthly in obese versus non-obese patients with schizophrenia.

**Source of Funding:** Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S

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### **THE EFFECTS OF CALORIC VESTIBULAR STIMULATION ON ILLNESS AWARENESS IN SCHIZOPHRENIA: A PILOT, PROOF OF CONCEPT STUDY**

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**Introduction:** Anosognosia or impaired insight into illness is common among individuals with schizophrenia contributing to medication non-adherence and poor treatment outcomes. Caloric vestibular stimulation (CVS) is typically used to assess functioning of the peripheral vestibular organ, specifically, the horizontal semicircular canal. CVS is transiently effective treatment for anosognosia and hemineglect secondary to right brain hemisphere stroke. There are only a few case reports of insight improvement and mood stabilization with left cold CVS in patients with schizophrenia spectrum or bipolar disorders. **Methods:** Subjects with a schizophrenia spectrum disorder and moderate-to-severe insight impairment ( $\geq 3$  PANSS G12) participated in a double blind, crossover, randomized controlled proof of concept study of the effects of CVS on insight into illness. Subjects sequentially received all experimental conditions—left cold (4°C) CVS, right cold CVS, and sham/body temperature—in a random order. Insight into illness was assessed using the VAGUS, Self-report and Clinician-Rated versions (VAGUS-SR and VAGUS-CR). Positive symptoms were assessed using the SAPS, and a 10-point Likert scale was used to assess mood. Assessments were performed pre-CVS, 5 min, and 30 min post-CVS. **Results:** Data from 13 subjects (PANSS G12,  $x=4.5$ ,  $SD=1.0$ ) were analyzed at 30 min post-CVS. VAGUS-SR Insight improvement: Left\_cold\_CVS>Sham, Cohen's  $d=0.09$ ; Right\_cold\_CVS>Sham,  $d=-0.31$ ; Left>Right\_cold\_CVS,  $d=0.40$ ; VAGUS-CR Insight improvement: Left\_cold\_CVS>Sham,  $d=0.09$ ; Right\_cold\_CVS>Sham,  $d=-0.05$ ; Left>Right\_cold\_CVS,  $d=0.13$ ; Mood improvement: Left\_cold\_CVS>Sham,  $d=0.88$ ; Right\_cold\_CVS>Sham,  $d=0.07$ ; and Left>Right\_cold\_CVS,  $d=0.92$ . **Conclusions:** Left cold CVS appears to transiently improve insight into illness and elevate mood in schizophrenia spectrum disorders. The procedure's effectiveness is thought to be due to the stimulation of inactive right hemisphere circuits via vestibular nuclei projections to the contralateral hemisphere when using left cold CVS. Treatment studies over an extended duration of time (e.g. daily x 5 - 10 days) are required to determine the procedure's efficacy for improving illness awareness in schizophrenia.

**Learning Objectives:**

- To understand the role of hemispheric rivalry in illness awareness.
- To learn about the effects of caloric vestibular stimulation on insight into illness.

**Source of Funding:** Ontario Mental Health Foundation

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**COMPARATIVE OUTCOMES AFTER SWITCHING FROM RISPERIDONE LONG-ACTING INJECTABLE TO PALIPERIDONE LONG-ACTING INJECTABLE OR ORAL ANTIPSYCHOTICS**

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**Introduction:** Evidence suggests that, under some circumstances, switching antipsychotic (AP) medications may put patients at greater risk for relapse. This report examines the relapse risk following switch from risperidone long-acting injectable (RLAI) to another long-acting injectable AP (paliperidone palmitate [PP]) versus switch to an oral AP. **Methods:** The Truven MarketScan Multi-State Medicaid (MSM) database, which captured medical and pharmacy claims for 11.6M beneficiaries between 2006 and 2011, was used to compare relapses (measured by schizophrenia-related inpatient hospitalizations and emergency department [ED] visits) following switches from RLAI. New user cohorts for these 2 groups were created based on the first incidence of exposure to the “switched to” drug. Groups were balanced using 1-to-1 propensity score matching. Patients were required to have a prior diagnosis of schizophrenia and an observed switch in therapy on or after July 31, 2009 (US approval date for PP). Time-to-event analysis was used to assess schizophrenia-related inpatient admissions or ED visits. **Results:** 187 patients who switched from RLAI to PP were identified, along with 128 patients who switched from RLAI to an oral AP. Propensity score modeling was used to select 5 important predictors of treatment: age, number of concomitant medications, number of prior outpatient visits, number of schizophrenia-related visits, and number of days on antipsychotic treatment. Matching diagnostics suggest that the cohorts were sufficiently balanced for all modeled covariates and most unmodeled covariates. The final matched cohort included 109 patients who switched to PP and 109 patients who switched to an oral AP agent. Patients who switched from RLAI to PP had fewer events (27 vs 30), had longer time to an event (mean of 72 vs 44 days), remained on the new medication longer (mean of 236 vs 126 days), and had lower risk of relapse (HR 0.58, 95% CI 0.34-0.99, P=0.047) compared with those switched from RLAI to an oral AP. **Conclusions:** This claims database study of real-world patients with schizophrenia suggests that switching from RLAI to PP may be associated with lower risk for relapse and longer duration of therapy compared with switching to an oral AP. Given the potential sources of error in observational studies and the extent to which the risk of residual confounding would impact the findings, these results cannot be viewed as definitive and should be confirmed by evaluations in other settings. **References** Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. *Eur Psychiatry* 2010; 25(suppl 2):S12-21. Hawley C, Turner M, Latif MA, Curtis V, Saleem PT, Wilton K. Switching stable patients with schizophrenia from depot and oral antipsychotics to long-acting injectable risperidone: reasons for switching and safety. *Hum Psychopharmacol* 2010; 25(1):37-46.

**Learning Objectives:**

- To educate participants on the issue of switching patient medications and the increased risk for relapse.
- To educate participants on the relapse risk of switching from a long-acting injectable (LAI) antipsychotic (AP) to another LAI versus switching from an LAI to an oral AP.

**Source of Funding:** Support: Janssen Scientific Affairs, LLC

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## **EXPLORING NEUROPATHOLOGICAL DEFICITS AND NEW DRUG TARGETS FOR MAJOR PSYCHIATRIC DISORDERS USING THE STANLEY NEUROPATHOLOGY CONSORTIUM DATASETS AND RNA-SEQ DATA**

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The Stanley Neuropathology Consortium Integrative Database (SNCID, <http://sncid.stanleyresearch.org>) is a data-mining tool that includes 3586 neuropathological data sets as well as raw RNA-Seq data measured in two sample collections. The data can be used to further understand the aetiology of major psychiatric diseases and to potentially identify new drug targets for these disorders. The two collections include the Neuropathology Consortium, which consists of 15 well-matched cases in each of four groups: schizophrenia (SCH), bipolar disorder (BPD), depression (MD) and unaffected controls (UC), and the Array Collection, which consists of 35 cases in each of three groups: SCH, BPD and UC. We reanalysed the neuropathological markers in multiple brain regions to identify those abnormalities that are shared between psychiatric disorders and those that are specific to each disorder. We then performed gene co-expression network analyses to identify the co-expression modules associated with each disease and also with abnormal markers in the hippocampus using the RNA-Seq data. Of the 2672 consortium collection data sets, 254 showed a significant abnormality in at least one disorder as compared to UCs. In the cortex, perineuronal oligodendrocytes and related markers were significantly altered in all three groups; SCH, BPD and UC whereas, the density of parvalbumin-containing neurons and related markers were significantly altered in just SCH and BPD, as compared to UCs. In the hippocampus, reelin-containing neurons and related markers were abnormal in the all three disease groups, whereas the density of parvalbumin-containing neurons and related markers were altered in SCH and BPD only. Co-expression modules that included immune and inflammation related genes were associated with SCH and BPD but not with MD. The immune/inflammation modules were also associated with the density of parvalbumin-containing neurons. The increased expression of immune and inflammation-related genes in the hippocampus may contribute to the deficits in the parvalbumin-containing neurons in SCH and BPD. The data further supports the possibility that drugs that impact the immune/inflammation system may be beneficial for the treatment of SCH and BPD.

### **Learning Objectives:**

- Understand neuropathological abnormalities that are shared between major psychiatric disorders.
- Identify the co-expression modules associated with each disease and also with abnormal markers in the hippocampus using the RNA-Seq data.

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## **CLOZAPINE MAY EXERT ITS SUPERIOR EFFICACY ON SCHIZOPHRENIA THROUGH ITS SEROTONIN 5HT2C RECEPTOR INVERSE-AGONISM**

*Hidehiro Oshibuchi*

*UCSF*

Clozapine may exert its superior efficacy on schizophrenia through its serotonin 5HT<sub>2C</sub> receptor inverse-agonism. Although clozapine provides improved efficacy relative to typical antipsychotics in treatment-resistant schizophrenia, the mechanisms through which the therapeutic benefit arise are not fully understood. To clarify the differences between antipsychotics, I examined the effects of the antipsychotics on the time course changes of basal dopamine release and the fear-conditioned cue induced dopamine release in the amygdala of methamphetamine-sensitized rats using in-vivo microdialysis and HPLC techniques, then reported the following findings. 1) Antipsychotics increase basal dopamine release in the amygdala of naïve rats (no methamphetamine pre-treatment). The magnitude of the increase is greater for clozapine than for haloperidol. 2) Haloperidol increases basal dopamine release also in the amygdala of methamphetamine-sensitized rats while clozapine does not elicit the increased basal dopamine release in the sensitized rats. 3) Antipsychotics attenuate phasic amygdala dopamine release in response to fear conditioned cues in the amygdala both of the naïve and methamphetamine-sensitized rats. The magnitude of the attenuation is greater for clozapine than for haloperidol. Clozapine binds to D<sub>2</sub>Rs with very low affinity and acts at the multiple molecular targets (Richtab, 2007). Serotonin 2C receptor subtypes (5HT<sub>2CRs</sub>) are one of the binding sites of clozapine with high affinity as inverse agonist. The 5HT<sub>2CRs</sub> exert an overall inhibitory influence over the dopamine mesoaccumbens pathway via an activation of GABA interneurons. However, the 5HT<sub>2CR</sub> has also been identified within dopaminergic neurons (Bubar, 2007). Interestingly, local 5HT<sub>2CRs</sub> antagonist, SB242084 injection into the NAC reversely inhibits cocaine-induced dopamine release in the NAC. The inhibiting effect of SB242084 is enhanced in cocaine-sensitized rats (Zayara, 2011). Further, 5HT<sub>2CRs</sub> in the NAC are functionally upregulated under sensitized conditions (Yoshimoto, 2012). Thus, combining these findings, I hypothesize that 1) pathogenesis of dopaminergic sensitization involves 5HT<sub>2CR</sub>'s functional upregulation in the NAC, and 2) the unique action of clozapine interacting with upregulated 5HT<sub>2CRs</sub> in the NAC as inverse agonist accounts for its superior therapeutic benefits. To address the hypotheses, a critical issue that must be clarified is the relative contributions of two 5HT<sub>2CR</sub> subpopulations expressed on the dopamine neurons and on the GABA neurons in the NAC and VTA to the regulation of mesoaccumbens dopamine release under sensitized conditions. Toward this end, now I am studying mice bearing region-specific inactivation of 5HT<sub>2CRs</sub> restricted to GABA neurons by taking advantage of Cre-loxP conditional inactivation. Using the mutants, I will clarify the pathogenesis of sensitization to psychostimulants and distinguish functions between the two 5HT<sub>2CR</sub> subpopulations by local clozapine injection into the NAC and VTA under sensitized conditions. The findings of the current study would facilitate the development of novel treatment strategies for psychotic disorders. In order to optimize my effectiveness in the conduct of such translational research, keeping abreast of the latest biological and clinical perspectives is essential. No meeting serves this goal better than the NCDEU new investigator award of the ASCNP annual meeting.

### **Learning Objectives:**

- To learn about the significance of dopamine-serotonin interaction in the efficacy of clozapine.
- To learn about the various serotonin-based treatment for the symptoms of schizophrenia.

**Source of Funding:** Larry Tecott. M.D. Ph.D (University of California, San Francisco)

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**AN OPEN-LABEL EXTENSION STUDY OF LURASIDONE SAFETY AND EFFICACY IN PATIENTS WITH SCHIZOPHRENIA PREVIOUSLY RANDOMIZED TO LURASIDONE OR RISPERIDONE**

*Gregory Mattingly<sup>1</sup>, Michael Tocco<sup>2</sup>, Debra Phillips<sup>2</sup>, Jane Xu<sup>2</sup>, Andrei Pikalov<sup>2</sup>, Antony Loebel<sup>2</sup>*  
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**Background and Objective:** Treatment response to antipsychotic medication can show wide interindividual variation, and patients have differing propensity for and tolerance of adverse effects. 1 Thus, switching antipsychotic treatments to achieve an optimal balance of efficacy and tolerability is common in clinical practice.2 The objective of this study was to evaluate the safety and efficacy of lurasidone in patients with chronic schizophrenia who continued on lurasidone (LUR-LUR) or switched from risperidone (RIS-LUR). **Methods:** Patients completing a 12-month, randomized, double-blind study evaluating flexibly dosed lurasidone (40-120 mg/d) versus risperidone (2-6 mg/d) entered a 6-month, open-label extension (OLE) study with flexibly dosed lurasidone (40-120 mg/d; ClinicalTrials.gov identifier: NCT00641745). Descriptive statistics evaluated safety and efficacy using last observation carried forward (LOCF) and observed case (OC) approaches. **Results:** Among 223 patients (136 LUR-LUR, 87 RIS-LUR) who continued into the OLE study, overall discontinuation rates were 19.9% for LUR-LUR and 25.3% for RIS-LUR. Mean (SD) change in weight from OLE baseline to endpoint (OC) was -0.6 kg (3.3 kg) for LUR-LUR and -2.9 kg (5.4 kg) for RIS-LUR patients. Median changes in metabolic parameters from OLE baseline to endpoint (OC) for LUR-LUR vs RIS-LUR patients were: -4.0 mg/dL vs 4.5 mg/dL for total cholesterol, -4.5 mg/dL vs -5.5 mg/dL for triglycerides, and 0.0 mg/dL vs -3.0 mg/dL for glucose. Prolactin levels showed little change in LUR-LUR patients (median change from OLE baseline to endpoint [OC]: men, 0.2 ng/mL; women, 1.3 ng/mL) and decreased in RIS-LUR patients (men, -11.2 ng/mL; women, -30.8 ng/mL). During the OLE, extrapyramidal symptom-related treatment-emergent adverse events (TEAEs) were noted in 8.1% of LUR-LUR and 6.9% of RIS-LUR patients; akathisia and somnolence each occurred in 3.7% of LUR-LUR patients and 2.3% of RIS-LUR patients. Discontinuation from the OLE due to a TEAE occurred in 5.1% of LUR-LUR and 6.9% of RIS-LUR patients. At OLE baseline, mean (SD) scores on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity (CGI-S) were 55.5 (12.7) and 2.9 (0.8), respectively. In both the LUR-LUR and RIS-LUR groups, mean change from OLE baseline (LOCF) was 1.0 on the PANSS and 0.0 on the CGI-S. **Conclusion:** Switching to lurasidone after 12 months of treatment with risperidone was generally safe and well tolerated, with improvement in weight and prolactin levels, in this 6-month OLE study. Patients who transitioned from risperidone to lurasidone maintained clinical stability.

**References:**

- Zhang J-P & Malhotra AK. Expert Opin Drug Metab Toxicol 2011; 7:9-37
- de Smidt C et al, Eur J Psychiatry 2012; 26:41-49

**Learning Objectives:**



- Describe the safety profile of lurasidone in patients with schizophrenia over long-term treatment and after switching from risperidone.
- Describe the efficacy of lurasidone after switching from risperidone.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals, Inc.

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## **CORRELATES OF SOCIAL COGNITION AND NEUROCOGNITION TO FUNCTIONAL OUTCOMES**

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Background: Deficits in social functioning, including communication, work, social skills, and community functioning, are a defining feature of schizophrenia. Functional outcomes of schizophrenia are affected by several factors such as social cognition, neurocognition, psychopathology, and clinical outcomes. The multifaceted association among these factors and functional outcome continues to be unclear. Given the significant role of functional outcomes in schizophrenia, there has been increasing importance in factors that may underlie these outcomes. If the characteristics of these factors can be defined, interventions may be developed to improve them, which, in turn, will have a parallel impact on long term functioning and outcome. The current study examines whether social cognition, neurocognition and clinical symptoms have a relationship on functional outcomes in patients with schizophrenia. Methods: 45 patients with DSM-IV schizophrenia were assessed for: Neurocognition; MCCB-MATRICES, Clinical Symptoms: PANSS, Social Cognition: MSCEIT, Emotion Recognition-40 (ER-40), Dynamic Social Cognition Battery (DSCB: Emotion Identification – Facial, Verbal and Non Verbal), Functional Outcomes: University of San Diego Performance Based Assessment (USCD-UPSA), Social Skills: Personal and Social Performance Scale (PSP). Structural Equation Modeling (SEM) employed with maximum likelihood estimation for test effects. Results: The overall model fit was  $\chi^2=39.8$ ,  $P<0.14$ . Fit indexes: Cmin/df=1.27, NFI=0.95, Tucker–Lewis index (Bentler and Bonnet nonformed fit index)=0.96, RMSEA=0.049. Regression weights of the latent variable “Marder Negative Factor” were significant and high ( $\beta=0.92$ ) and a substantial amount of variance could be explained by negative symptoms, indicating that the negative factor is a reliable measure of the latent variable. In addition, the regression weights of the latent variable social cognition to the 3 indicators were moderate and significant (Emotion Recognition DSCB:  $\beta=0.77$ , ER-40:  $\beta=0.46$ , and Nonverbal Emotion Identification,  $\beta=0.45$ ). Like social cognition, the latent variable functional assessment explained a substantial amount of variance in the latent variables of working memory (45%). Impact of social cognition on negative symptoms ( $\beta=0.91$ ) was greater than the direct impact of social functioning ( $\beta=0.78$ ) and functional assessments ( $\beta=0.63$ ). Conclusions: This study suggests that 49% of negative symptoms could be explained by impaired social cognition and that 49% of social functioning skills could be explained by social cognition. Our findings suggest that social cognition may be an essential target to improve functional outcomes. These findings provide evidence that may help develop novel interventions.

## **Learning Objectives:**

- The audience will learn how social cognition and neurocognition can effect functional outcomes.
- The audience will be able to understand how novel analytic techniques can be utilized to assess correlates among neurocognition, social cognition, and functioning.

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**A RANDOMIZED BLIND PARALLEL INTRAMUSCULAR HALOPERIDOL-CONTROLLED MULTICENTER CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF INTRAMUSCULAR LEVOSULPIRIDE IN THE TREATMENT OF CHINESE PATIENTS WITH AGITATION OF SCHIZOPHRENIA**

*Yifeng Shen, Huafang Li*

*Shanghai Mental Health Center*

**PURPOSE:** The aim of this study is to compare efficacy and safety of Intramuscular Levosulpiride in the treatment of Chinese patients with Agitation of Schizophrenia with Intramuscular Haloperidol. **METHODS:** This study was conducted in 5 sites in China. All patients or his/her legal representatives were required to provide written informed consent. Eligible patients were inpatients within 18-65 years old, with a DSM-IV criteria for schizophrenia or schizophreniform psychosis, agitated with a minimum total score of  $\geq 15$  on PANSS-EC and at least one individual item score of  $\geq 5$  or two item score of  $\geq 4$ . All eligible patients were randomized to 3 days of blind treatment with Intramuscular Levosulpiride (50mg Bid) or Intramuscular Haloperidol (5mg Bid). The primary efficacy endpoint was defined as the change from baseline to 72 hours in the PANSS-EC total score. Additional efficacy parameters were CGI, ACES, PANSS and BPRS. Response was defined as a  $\geq 50\%$  decrease in the PANSS-EC. Safety and tolerability were evaluated on the basis of adverse events, RSESE, BAS, ECGs, vital signs, and laboratory tests. **RESULTS:** A total of 199 patients entered the study (100 vs 99). A total of 196 patients completed the study (99 vs 97). One patient withdrew informed consent in the Levosulpiride group and 2 patients withdrew due to adverse events in the Haloperidol group. Two patients in the Haloperidol group had serious protocol violation. The PPS thus comprised 99 vs 95. There were no clinically relevant differences at baseline between the two treatment groups on the basis of demography or disease severity. The mean PANSS-EC total score decreased substantially over time for patients in both treatment groups. However, there was no significant difference between 2 groups. The responders in both treatment groups were approximately equal (47.00% vs 61.62%). A total of 36.00% of patients in the Levosulpiride group and 56.57% of the patients in the Haloperidol group reported AEs with significant difference ( $P=0.0036$ ). Similarly, there were 29.00% patients in study group experienced adverse reactions and 49.49% in controlled group. Especially, there were distinct difference incidence in acute dystonia between 2 groups (4.00% vs 15.15%,  $P=0.0074$ ). However, there were no apparent trends within or between treatment groups with respect to laboratory values, ECG or vital signs. **DISCUSSION:** The study showed clear treatment-related improvements in PANSS-EC scores in both treatment groups. The efficacy of Levosulpiride (50mg Bid im) was similar to Haloperidol (5mg Bid im). And this study also supported the opinion that Levosulpiride had the similar responder profile as typical antipsychotics. This study also has been suggested that Intramuscular Levosulpiride was associated with less EPS. The reason of no significant difference in other adverse reactions could be found might be in relative small sample. In conclusions, this study showed Intramuscular Levosulpiride was an effective safe antipsychotic for Chinese adult patients with Agitation of Schizophrenia.

### **Learning Objectives:**

- To share efficacy and safety information of Intramuscular Levosulpiride.
- To learn China treatment clinical trial in the patients with Agitation of Schizophrenia.

**Source of Funding:** China National Science and Technology Major Project for IND in psychiatry (2012ZX09303-003)

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### **VARENICLINE EFFECTS ON SMOKING, COGNITION, AND PSYCHIATRIC SYMPTOMS IN SCHIZOPHRENIA: RESULTS OF A DOUBLE-BLIND PLACEBO CONTROLLED STUDY**

*Robert C. Smith*

*NYU School of Medicine and Nathan Kline Institute for Psychiatric Research*

Introduction: Schizophrenics have a high rate of smoking and cognitive deficits which may be related to a decreased number or responsiveness of nicotinic receptors in their brains. Varenicline is a partial nicotinic agonist which is effective as an antismoking drug in normals, although concerns have been raised about potential psychiatric side-effects. Nicotinic agonists or partial agonists have been proposed as potential treatments for cognitive deficits in schizophrenia. We conducted a double-blind placebo controlled study to evaluate effects of varenicline on measures of smoking, cognition, psychiatric symptoms, and side-effects in schizophrenic patients who were cigarette smokers. Methods: 87 patients with diagnosis of schizophrenia or schizoaffective disorder at 4 sites (2 US, 1 Israel, and 1 China) participated in a double-blind placebo-controlled study in which they received varenicline (2 mg/day) or matched placebo for 8 weeks, with some sites extending selected measures to 12 weeks. All subjects received brief weekly structured behavioral counseling sessions on smoking cessation. Smoking was evaluated with objective measures of breathalyzer CO, and serum nicotine and cotinine, and self-report measures of cigarettes smoked and a smoking urges scale. Cognition was measured by MATRICS cognitive battery. Psychiatric symptoms were evaluated with PANSS, SANS, and Calgary Depression scales. Side effects were evaluated with a side-effect check list and additional probing questions for suicidal and depressive thoughts. Statistical analysis used SAS mixed model ANCOVA (baseline covariate) and SPSS GLM ANCOVA supplied by other analyses. Results: Varenicline significantly decreased objective measures of smoking, and responses on a smoking urges scale, more than placebo. However, only 22-24% of varenicline subjects had measures indicating they had quit smoking by 8 weeks, and these 'quit' percentages did not differ between varenicline and placebo. Varenicline did not improve either overall MATRICS Composite scores or summary scores on Cognitive Domain. Placebo patients improved significantly more than varenicline patients on Reasoning and Problem Solving domain. Varenicline patients tended to improve more on Trial Making Test Part A. There were no significant differences between varenicline and placebo on total scores on PANSS, SANS, or Calgary Depression Scale. There was no increase in any measure of psychiatric symptoms with varenicline, and varenicline patients showed trends for decrease in symptoms scores on several measures (although the decreases were not significantly greater than placebo for most measures). Varenicline patients showed a significantly greater decrease in PANSS Depression Factor sub-score than placebo patients, and had a greater decrease in SANS Avolition sub-score. Varenicline patients did not show greater side-effects than placebo treated patients at any time point. Conclusions: Varenicline was a safe and effective drug for decreasing cigarette smoking in schizophrenic patients. It was not a

cognitive enhancer on the MATRICS battery measure. It did not increase psychiatric symptoms and may decrease some components of depression or negative symptoms in schizophrenic patients.

### **Learning Objectives:**

- Discuss the efficacy of varenicline as a treatment for cigarette smoking in patients with schizophrenia.
- Assess whether varenicline has risks of increasing psychiatric symptoms, depression or suicide risk in patients with schizophrenia.
- Discusses the underlying biological rationale which makes nicotinic agonists candidates for drugs which may improve cognition in schizophrenia.

**Source of Funding:** Stanley Foundation Grant/ funded the study. Pfizer provided active and placebo varenicline drug.

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### **PALIPERIDONE RESEARCH IN DEMONSTRATING EFFECTIVENESS (PRIDE): MANAGING SCHIZOPHRENIA PATIENTS WITH A HISTORY OF INCARCERATION**

*H. Lynn Starr<sup>1</sup>, Larry Alphs<sup>2</sup>, Lian Mao<sup>3</sup>, Stephen Rodriguez<sup>4</sup>*

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**Background:** The management of patients with schizophrenia is often complicated by comorbid medical conditions such as substance use, which is associated with more severe and treatment-resistant schizophrenia, longer hospital stays, and increased risk of criminal justice system (CJS) involvement. This analysis examines the impact of substance use on treatment failure in subjects with schizophrenia and a history of CJS involvement who were receiving antipsychotic treatment. **Methods:** This exploratory analysis of an interim database utilized blinded data from the Paliperidone Research in Demonstrating Effectiveness (PRIDE) study, a recently completed 15-month, randomized, open-label, rater-blinded, multicenter, US study comparing paliperidone palmitate with oral antipsychotics in a community sample of schizophrenia subjects with a history of incarceration (NCT01157351). Substance users were identified by endorsing lifetime or prior 30-day use on the Alcohol/Drug Use Questionnaire (ASI-Lite), administered at the baseline visit. Distribution to the “time to treatment failure” (defined as arrest/incarceration, psychiatric hospitalization, suicide, treatment discontinuation or supplementation due to inadequate efficacy, safety, or tolerability, or increased psychiatric services to prevent hospitalization) was estimated by Kaplan-Meier. **Results:** As of 8/18/2013, 450 subjects were included; 280 (62.2%) were substance users, and 170 (37.8%) were not substance users. Mean (SD) age in the substance use and no substance use cohorts: 36.9 (10.3) and 40.0 (10.5) years, respectively; proportions of males: 87.1% and 59.3%, respectively. Median (95% CI) time to treatment failure was 198 days (143-291) in the substance use cohort and greater than 450 days in the no substance use cohort. Kaplan-Meier median (95% CI) time to first arrest or psychiatric hospitalization in those with versus without substance use was 321 days (210-444) and greater than 450 days, respectively. Most common adverse events ( $\geq 10\%$  in each cohort) in the substance use versus no substance use cohorts were insomnia (16.1% vs 12.9%), akathisia (10.4% vs 7.6%), anxiety (10.0% vs 8.8%), and depression (10.0% vs 4.7%). **Conclusions:** In

this clinical trial dataset of schizophrenia subjects with a history of incarceration, more than half were identified as substance users based upon the ASI-Lite scale. Substance use was associated with shorter time to and higher rate of treatment failure.

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#### Learning Objectives:

- To educate participants on the incidence of psychiatric disorders within the criminal justice system.
- To evaluate the impact of substance use on treatment failure in subjects with schizophrenia and a history of criminal justice system involvement who were receiving antipsychotic treatment.

**Source of Funding:** Support: Janssen Scientific Affairs, LLC

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#### **A RANDOMIZED, PLACEBO-CONTROLLED REPEAT-DOSE THOROUGH QT STUDY OF INHALED LOXAPINE IN HEALTHY VOLUNTEERS**

*James V. Cassella<sup>1</sup>, Daniel A. Spyker<sup>1</sup>, Paul P. Yeung<sup>2</sup>*

*<sup>1</sup>Alexza Pharmaceuticals, Inc., <sup>2</sup>Teva Pharmaceuticals*

**Objective:** To investigate potential effects on cardiac repolarization (QT-interval) of 2 consecutive doses of inhaled loxapine administered 2 hours apart (NCT01854710). **Background:** Single-dose administration of inhaled loxapine via the Staccato® system (1) was not associated with clinically relevant QT prolongation (2), but the effect of repeat dosing of inhaled loxapine on QTc prolongation has not been previously studied. **Design/Methods:** This randomized, double-blind, positive-controlled, cross-over study was conducted in healthy volunteers 18 to 65 years of age. Each subject received: 2 doses of inhaled loxapine (10mg) + oral placebo; 2 doses inhaled placebo + oral placebo; or 2 doses inhaled placebo + oral moxifloxacin (400mg) [positive control], with at least 3-days washout between treatments. Inhaled doses were given 2 hours apart. The primary outcome was maximum effect of inhaled loxapine on QTc interval duration compared with placebo at 12 preselected time points across a 24-hour post-dose interval. **Results:** Of 60 enrolled subjects (mean age 33.8 years; 52% male), 45 (75%) completed the study. Inhaled loxapine did not significantly increase QT interval across the 24-hour post-dose follow-up, as demonstrated by a maximum mean increase of 4.04 msec in the placebo-corrected change in QTc from baseline, with an upper 95% CI of 6.31 msec at 5 minutes after the second-dose. As a positive control, the lower one-sided 95% CI for moxifloxacin effect was >5 msec at all 4 predefined post-dose time points. **Conclusions:** No clinically relevant change in QTc was seen with multiple doses of inhaled loxapine in this population of healthy volunteers. Inhaled loxapine did not significantly prolong the QTc interval in this study. These results of this study suggest that inhaled loxapine is not associated with cardiac re-polarization liability.

Literature References: 1. Spyker DA, Munzar P, Cassella JV. Pharmacokinetics of loxapine following inhalation of a thermally generated aerosol in healthy volunteers. *J Clin Pharmacol* 2010; 50:169-179. 2. Spyker DA, Voloshko P, Heyman ER, Cassella JV: Loxapine delivered as a thermally generated aerosol does not prolong QTc in a thorough QT/QTc study in healthy subjects. *J Clin Pharmacol*. 2013; doi: 10.1002/jcph.257.

### **Learning Objectives:**

- To understand the pharmacodynamic effects on cardiac repolarization of multiple doses of inhaled loxapine via a thorough QTc study.
- To discuss original research relevant to the cardiac safety of inhaled loxapine.

**Source of Funding:** Study funded by Alexza Pharmaceuticals. Medical writing support, funded by Teva Pharmaceuticals, was provided by Karen Burrows, MPhil, of Excel Scientific Solutions.

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### **LAMOTRIGINE: ARE WE DOSING IT OPTIMALLY IN PREGNANT WOMEN WITH BIPOLAR DISORDER?**

*Crystal T. Clark*

*Northwestern University Feinberg School of Medicine*

Objective: Lamotrigine (LTG) is an antiepileptic drug that is FDA indicated for the maintenance treatment of Bipolar Disorder (BD). It has emerged as a first-line option for childbearing women with epilepsy due to its favorable reproductive profile. Observational studies of WWE show that LTG level-to-dose (L/D) ratios decline during pregnancy and result in increased seizure frequency. Thus, dosing algorithms have been developed to advise increases in LTG dose during pregnancy and decrease seizure recurrence. Similar to WWE, pregnancy is a vulnerable time for BD. Discontinuation of mood stabilizing medication increases the risk of BD symptom and syndromal recurrence. LTG is an option for maintaining wellness in pregnant women with BD. Although, the benefit of continuing LTG in pregnancy may outweigh the risk for some women with Bipolar Disorder, unlike WWE, there is minimal information to inform dosing, or the utility of therapeutic dose monitoring. Information on pharmacokinetic changes of lamotrigine (LTG) in pregnant women with Bipolar Disorder is limited. Data is presented on serial serum levels of LTG in pregnant patients with Bipolar Disorder using monotherapy during pregnancy.

Comparative postpartum LTG serial serum levels were obtained in addition to levels in the umbilical cord and in infants exposed to LTG through breastmilk. Neurology data is reviewed as it relates to the data presented. Methods: LTG serum samples were obtained from eight mother-infant pairs at different time points during pregnancy and postpartum. Results: All of the women were taking LTG throughout childbearing. Level-to-dose (L/D) ratios were lower in pregnancy than postpartum and, for two patients, L/D ratios reached the lowest serum level in the third trimester. LTG doses were taken once daily and ranged from 100 to 300mg. Three patients had an increase of 50mg to their daily dose across pregnancy. The change in LTG concentrations postpartum ranged from a 30% decrease to a 640% increase compared to the first level obtained in pregnancy. Level-to-dose (L/D) ratios obtained within 4 weeks postpartum reflected a mean of 402% greater than the baseline gestational levels. Compared to third trimester, LTG serum concentration increased an average of 154% within 5 weeks postpartum. The most dramatic increase in the LTG serum level early after birth at 1.5 weeks postpartum. The mean infant cord level was 66% of the maternal serum level at delivery. The mean breast-fed infant serum level was 32.5% of the maternal serum levels. Conclusion: The pattern of LTG changes during

pregnancy and postpartum in these women with Bipolar Disorders was consistent with that described in the neurology literature.

**Learning Objectives:**

- The effects of pregnancy on LTG concentration in pregnant women with Bipolar Disorder.
- Considerations for dosing LTG postpartum to prevent toxicity as it relates to LTG concentration.

**Source of Funding:** Supported in part by Grant Number K12 HD055884 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development

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**SEXUAL SYMPTOMS ASSOCIATED WITH LEUPROLIDE ACETATE THERAPY IN INFERTILITY PATIENTS TREATED FOR ENDOMETRIOSIS**

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*<sup>1</sup>University of Oklahoma-HSC- Tulsa, <sup>2</sup>The University of Oklahoma College of Medicine Tulsa - School of Community Medicine*

Declines in gonadal steroids occurring during various reproductive life events such as menopause, following bilateral oophorectomy, or with certain medications such as leuprolide or aromatase inhibitors which may impact a woman's vulnerability to sexual symptoms. Women with endometriosis undergoing significant declines in sex steroids during leuprolide acetate therapy, a form of gonadotropin-releasing hormone (GnRH) agonist therapy, are hypothesized to report an increase in sexual symptoms. Methods: Fifty-six premenopausal patients with endometriosis, ages 19 to 40, were evaluated at baseline, prior to leuprolide acetate therapy (3.75mg IM Q 28 days), and at months 1, 2, and 5. Sexual symptoms were evaluated using the Menopause Symptom Index (MENSI). Results: A t-test for dependent samples indicated a statistically significant increase a variety of menopausal physical and psychiatric symptoms from baseline to: month 1 MENSI ( $t=6.89$ ,  $p<0.001$ ); month 2 MENSI ( $t=10.62$ ,  $p<0.001$ ); month 5 MENSI ( $t=8.87$ ,  $p<0.001$ ). An item level chi-square analysis of the frequency of physical symptoms indicated that the chemical menopause induced in women with endometriosis during leuprolide therapy was associated with a significant increase in complaints of loss of sexual desire and vaginal dryness across five months of treatment. In addition, an increase in hot flashes, heart palpitations, headaches, sleep disturbance, numbness, and pain in bone joints were noted across five months of time. There was no change in pain with intercourse across the five months in these women with endometriosis. Conclusion: Leuprolide therapy in women is associated with an increase in sexual symptoms in women with endometriosis. The increase in sexual symptoms appears to be associated with leuprolide therapy and the decline in ovarian hormones. Lowered sex steroids are associated with symptomatic vulvovaginal dryness and atrophy which negatively affects sexual health.

**Learning Objectives:**

- Discuss the effects of lowered sex steroids and leuprolide on sexual function in women.
- Discuss the effects of estrogen on the vagina and the impact of estrogen levels on sexual desire, vaginal dryness and dyspareunia.

# Wednesday, June 18, 2014

## Poster Session 2

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### **A NOVEL COMPUTER-PROMPTED TANDEM RATING ASSESSMENT FOR ADULT ADHD CLINICAL TRIALS**

*Joan Busner<sup>1</sup>, Andrew J. Cutler<sup>2</sup>, Gary S. Sachs<sup>3</sup>, Dan DeBonis<sup>4</sup>, Timothy Hsu<sup>5</sup>, Catherine O'Brien<sup>5</sup>, Timothy Wilens<sup>6</sup>*

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Background: Variability in assessment of adult ADHD is a potential contributor to clinical trial failure. Particular challenges in adult ADHD trials include systematic application of childhood criteria to adult symptoms, and consistent scoring by eliciting and weighting frequency, severity, and impairment information. A computer administered adult prompted interview ( cADHD ) developed as a quality assurance tool for the ADHD-RS-IV rating scale was deployed in a single-blind with placebo run-in pilot study of an investigational compound (EB-1020-SR) conducted by expert investigators at three sites. The cADHD guides raters through the interview, providing prompted examples, selecting subsequent prompts, and ensuring that the rater obtains a standard minimum fund of information about symptom presence, frequency, severity, and impairment before rating each scale item; the cADHD also generates a second rating for each item. We report rater and computer generated cADHD baseline to endpoint change results from this pilot trial. Method. A computer-driven prompted interview was created for the 18 item ADHD-RS-IV and supplied to the three investigative sites conducting the study. For each item, site raters were computer-prompted as to symptom presence and then asked to enter data about pervasiveness, severity, and impairment. Prompts were based in part on a public-domain WHO adult adhd scale (ref). Programmed computerized follow-up question paths were driven by previous responses. Site raters chose and entered their own scores for each item. Unshown to the rater, the computer internally generated scores following a programmed algorithm based on the clinical characteristics the rater had input. Per protocol, the cADHD-prompted ADHD-RS rater scores served as the primary outcome measure. At the sponsor-determined interim analysis, cADHD rater and computer scores were analyzed and compared using Cronbach's alpha, and product moment correlations. Baseline to endpoint change was examined using paired t-tests. Baseline variability was examined through standard deviations. Results: 10 raters participated at the 3 sites and rated a total of 333 subject visits. Internal consistency of rater and computer cADHD total scores across visits was high (Cronbach's alpha=.92 and .89, respectively). Both rater and computer cADHD Total ADHD-RS scores showed a significant baseline to endpoint change (observed cases, N=37; baseline visit N=43) (see Figure), which occurred also for the Inattention and Hyperactivity/Impulsivity subscales scores (all ps < .0001). The correlations between rater and computer total and individual item scores were high (total=.94, individual items all greater than .80, mean=.87). Rater cADHD ADHD-RS-IV variability (baseline SD=6.91) was good in comparison to that reported in other clinical trials using the paper ADHD-RS-IV and other ADHD scales (e.g., Wilens et al, 2005; Adler, et al, 2009). Conclusions: The computer-prompted tandem assessment for adult ADHD showed feasibility as a rating aid and resulted in significant baseline to endpoint changes with good internal consistency and relatively



low variability in comparison to non-computer-prompted ADHD scales. The cADHD scale shows promise as a tool for improving ADHD ratings in clinical trials.

#### References:

- Wilens TE, et al. Biol Psychiatry 2005; 57:793-801 2) Adler LA, et al. J Clin Psychopharmacol 2009; 29:44-50

#### Learning Objectives:

- The attendee will become familiar with measurement issues in adult ADHD clinical trials.
- The attendee will become familiar with a novel computer-prompted ADHD scale used successfully in a pilot ADHD trial.

**Source of Funding:** Bracket

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#### EMOTIONAL DYSREGULATION AS AN ADULT ADHD SUBTYPE

*Frederick W. Reimherr<sup>1</sup>, Tammy A. Steans<sup>2</sup>, Kathleen Reimherr<sup>2</sup>, Phillip D. Gale<sup>2</sup>, Thomas Gift<sup>3</sup>, Paul H. Wender<sup>4</sup>, Barrie K. Marchant<sup>2</sup>*

<sup>1</sup>Psychiatric & Behavioral Solutions; University of Utah, <sup>2</sup>Psychiatric and Behavioral Solutions, <sup>3</sup>U of Rochester, <sup>4</sup>University of Utah

Background: Although DSM divides attention-deficit/hyperactivity disorder (ADHD) into 3 types (combined, predominately inattentive and predominately hyperactive), the decline in hyperactivity as patients age renders these categories much less useful in adults. Multiple studies show that patients with ADHD have significant emotional symptoms unaccounted for by other DSM diagnoses.<sup>1</sup> Such symptoms, which we've termed "emotional dysregulation"<sup>2</sup>, are assessed by the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)<sup>3</sup> and are part of the Utah Criteria for the diagnosis of ADHD in adults. These emotional symptoms are particularly prominent in adulthood and lead to the need for an alternative categorization of ADHD in adults. Methods: The WRAADDS consists of symptom items grouped into 7 domains. A factor analysis using principal components with varimax rotation was performed on WRAADDS domain scores from 762 adult ADHD patients. 2 factors emerged: an attention factor reflecting the domains of attention and disorganization and an emotional dysregulation factor reflecting the domains of restlessness/hyperactivity, temper, mood liability and emotional over-reactivity. Baseline patient characteristics associated with these factors and change over time were examined in 2 pooled clinical trials, each with an 8-week crossover methylphenidate/placebo phase followed by a 6-month open-label phase. "ADHD with emotional dysregulation" was defined using at least marked impairment on 3 of the 4 emotional domains. Results: 41% (n=56) of patients had elevated levels of symptoms as measured by the first factor alone compared to 59% (n=80) who were high on both factors. Psychopathology, including oppositional defiant disorder, personality disorder, substance misuse, and social maladjustment was more strongly associated with the emotional dysregulation factor. In the double-blind phase, both factors showed improvement (p<.001) with methylphenidate vs. placebo: Total WRAADDS (Cohen's d=.94) the attention/organization factor (d=.97) and the emotional dysregulation factor (d=.89). Conclusions: In adults, ADHD can be conceptualized as two major types: attention only and ADHD with emotional dysregulation. The diagnosis of

ADHD with emotional dysregulation is defined by at least marked impairment in 3 of the domains of: temper control, mood lability, emotional over-reactivity, and/or tension/restlessness. It is responsive to methylphenidate, and unlike the childhood hyperactivity/impulsivity category, this subtype remains prominent in adulthood.

#### References:

- Reimherr FW, Marchant BK, Strong RE, Hedges DW, Adler L, Spencer TJ, West SA, Soni P. Emotional dysregulation in adult ADHD and response to atomoxetine. *Biol Psychiatry*, 2005; 58(2):125-31.
- Barkley R A. Deficient emotional self-regulation: a core component of attention-deficit/hyperactivity disorder. *J ADHD & Related Disorders*, 2010;1(2), 5-37.
- Marchant BK, Reimherr FW, Robison D, Robison RJ, Wender PW. Psychometric properties of the Wender-Reimherr Adult Attention Deficit Disorder Scale. *Psychol Assess*, 2013; 25(3):942-50.

#### Learning Objectives:

- Attendees will be able to describe criteria for alternative (to DSM-V) categories of adult ADHD which includes symptoms of emotional dysregulation.
- Attendees will be able to describe the justifications for alternative diagnostic categories of adult ADHD.

**Source of Funding:** This reanalysis of data from two clinical trials was independently funded.

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### EMOTION RECOGNITION DEFICITS IN TREATED AND UNTREATED ADULT ADHD PATIENTS

*Anneka Tomlinson<sup>1</sup>, Robert Baskind<sup>2</sup>, Joe Johnson<sup>3</sup>, Kay Marshall<sup>1</sup>, Joanna C. Neill<sup>1</sup>*

*<sup>1</sup>University of Manchester, <sup>2</sup>Leeds and York NHS Foundation Trust, <sup>3</sup>5 Boroughs NHS Foundation Trust*

Introduction: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder now known to persist into adulthood. ADHD comprises of clusters of symptoms of inattention, impulsivity and hyperactivity. In adulthood ADHD presents a different profile compared with children, with fewer externalizing symptoms and higher rates of comorbidity. Both children and adults with ADHD have documented higher rates of impairments with regards to interpersonal and social functioning compared to those without ADHD. Deficits in emotional recognition during childhood have been proposed to underpin the social malfunctioning in ADHD. To date little is known about nonverbal emotion recognition in adults with ADHD, and in particular with respect to the subtypes of ADHD. Aims: 1. To compare the emotion recognition abilities in treated and untreated adults with ADHD and healthy controls. 2. To compare the emotion recognition abilities between the different subtypes of ADHD. Methods: Participants were recruited from two specialist National Health Service adult ADHD clinics in England. The sample consisted of 105 participants (men=66, women=49) divided into three groups: ADHD treated (ADHD-T; n=39), ADHD untreated (ADHD-UnT; n=42), and healthy controls (n= 24). The mean age was 29 years. All participants diagnosed with ADHD must have met the criteria outlined in DSM-IV. All ADHD participants completed a full self-report Connors Adult ADHD Rating Scale, WEISS-Global Impairment Rating Scale and five neurocognitive tasks using the Cambridge Automated Neuropsychological Test Battery (CANTAB). The Emotion Recognition

Task (ERT) – CANTAB task, was used to assess emotion recognition. ERT measures the ability to identify emotions in facial expressions. The participant was shown a series of faces, which appear on the screen briefly and were asked to identify the emotion (happiness, sadness, anger, disgust, surprise and fear). Computer-morphed images were derived from the facial features of real individuals each showing a specific emotion, are displayed on the screen. Results: ANOVA revealed that the ADHD-UnT group made more errors when presented with faces displaying fear, disgust and anger; relative to healthy controls ( $p < 0.001$ ). ANOVA also revealed that the ADHD-UnT group made more errors when presented with faces displaying disgust and anger, relative to ADHD-T ( $p < 0.001$ ). Finally, ADHD-T group made more errors when presented with faces displaying fear, disgust and anger, relative to healthy controls ( $p < 0.001$ ). Discussion: We have shown that adults with ADHD have impairments in facial emotion recognition in comparison to healthy controls. This study also provides evidence that standard ADHD medication (methylphenidate and/or atomoxetine), improves emotion recognition, specifically anger and disgust recognition. These findings highlight the importance of focusing on social cognition as a target for treatment and the importance of social functioning on the level of impairments in daily life of adults with ADHD. Future directions: We are still analysing data with respect to ADHD subtype differences, with the hypothesis to observe differences in correct responses in respect to three emotions: fear, disgust, anger.

#### **Learning Objectives:**

- To enhance the understanding recognition of ADHD in adulthood.
- To increase the understanding of the complex social cognitive deficits, specifically emotion recognition deficits in adult ADHD and the effects of medication on these deficits in social cognition.

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#### **ATTENUATION OF ETHANOL WITHDRAWAL BY CEFTRIAXONE-INDUCED UPREGULATION OF GLUTAMATE TRANSPORTER EAAT2**

*Ulas M. Camsari, Osama Abulseoud*

*Mayo Clinic*

Alcohol withdrawal syndrome (AWS) is a potentially fatal outcome of severe alcohol dependence that presents a significant challenge to treatment. Although AWS is thought to be driven by a hyperglutamatergic brain state, benzodiazepines, which target the GABAergic system, comprise the first line of treatment for AWS. Using a rat model of ethanol withdrawal, we tested whether ceftriaxone, a  $\beta$ -lactam antibiotic known to increase the expression and activity of glutamate uptake transporter EAAT2, reduces the occurrence or severity of ethanol withdrawal manifestations. After a 2-week period of habituation to ethanol in two-bottle choice, alcohol-preferring (P) and Wistar rats received ethanol (4.0 g/kg) every 6 h for 3-5 consecutive days via gavage. Rats were then deprived of ethanol for 48 h during which time they received ceftriaxone (50 or 100 mg/kg, IP) or saline twice a day starting 12 h after the last ethanol administration. Withdrawal manifestations were captured by continuous video recording and coded. The evolution of ethanol withdrawal was markedly different for P rats vs Wistar rats, with withdrawal manifestations occurring  $>12$  h later in P rats than in Wistar rats. Ceftriaxone 100 mg/kg per injection twice per day (200 mg/kg/day) reduced or abolished all manifestations of ethanol withdrawal in both rat variants and prevented withdrawal-induced escalation of alcohol intake. Finally, ceftriaxone treatment was associated with lasting upregulation of ethanol withdrawal-induced downregulation of EAAT2 in the striatum. Our data support the role of

ceftriaxone in alleviating alcohol withdrawal and open a novel pharmacologic avenue that requires clinical evaluation in patients with AWS.

**Source of Funding:** This work was supported by NIH/ NCRR CTSA KL2 (RR024151 to OAA) and was supported in part by Samuel C Johnson Genomics of Addiction Program at Mayo and by NIH (AA018779 to D-SC).

#### **Literature References:**

- Abulseoud OA, Miller JD, Wu J, Choi DS, Holschneider DP (2012). Ceftriaxone upregulates the glutamate transporter in medial prefrontal cortex and blocks reinstatement of methamphetamine seeking in a condition place preference paradigm. *Brain Res* 1456: 14–21.
- Alele PE, Devaud LL (2005). Differential adaptations in GABAergic and glutamatergic systems during ethanol withdrawal in male and female rats. *Alcoholism Clin Exp Res* 29: 1027–1034.

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#### **A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL ASSESSING THE EFFICACY OF VARENICLINE TARTRATE FOR ALCOHOL DEPENDENCE**

*Raye Z. Litten, Joanne B. Fertig, Daniel E. Falk, Megan L. Ryan*

*National Institute on Alcohol Abuse and Alcoholism, NIH*

**Objectives:** To assess the efficacy and safety of varenicline (Chantix) for the treatment of alcohol dependence. Varenicline is a partial  $\alpha 4\beta 2$  nicotinic acetylcholine agonist approved by the Food and Drug Administration for smoking cessation. It has reduced drinking in animal studies and in small studies of humans who were both heavy drinkers and smokers. This is the first multisite clinical trial of varenicline in a population of smokers and nonsmokers with alcohol dependence. **Methods:** Men and women ( $n = 200$ ) meeting the criteria for alcohol dependence were recruited across 5 clinical sites. Patients received double-blind varenicline or placebo and a computerized behavioral intervention. Varenicline was titrated during the first week to 2 mg/d, which was maintained during weeks 2 to 13. **Results:** The varenicline group had significantly lower weekly percent heavy drinking days (primary outcome) (adjusted mean difference = 10.4), drinks per day, drinks per drinking day, and alcohol craving compared with the placebo group ( $P < 0.05$ ). The average treatment effect on alcohol use was similar for smokers and nonsmokers. Varenicline was well-tolerated; adverse events were expected and mild. **Conclusions:** Varenicline significantly reduced alcohol consumption and craving, making it a potentially viable option for the treatment of alcohol dependence.

**Source of Funding:** Supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Contract No. HHSN27200900005C)

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#### **PROGESTERONE TREATMENT FOR POSTPARTUM COCAINE USERS**

*Kimberly Yonkers, Mehmet Sofuoglu, Kathleen Carroll*

*Yale School of Medicine*

**Background:** About 10% of women between the ages of 15 and 44 use illicit drugs, including cocaine. Illicit drug use drops markedly in pregnancy such that ~90% of women attain abstinence by delivery but most women relapse to drugs again postnatally. Many attribute the

decrease of illicit substance use in pregnancy to a mother's motivation to minimize her offspring's exposure to drugs. However, biological factors may also play a role. Progesterone production in pregnancy increases by a factor of 8 as compared to the follicular phase; it modulates multiple brain functions that may include addictive behaviors. In animals, progesterone diminishes a number of cocaine-enhanced behavioral responses including ambulation, rearing activity, conditioned placement preference, cocaine seeking and seizures. Human data, although limited, are largely consistent with preclinical studies in that there is an inverse relationship between endogenous progesterone levels and cocaine craving and use. Direct administration of progesterone to women diminishes cocaine-induced euphoria and cue-induced craving. The current study tested the efficacy of postpartum progesterone replacement as a treatment for cocaine addiction in postpartum women. Method: We recruited 50 postpartum women who abused cocaine either during the 6 months before or in pregnancy. Participants were randomized to receive either oral micronized progesterone (100 mgs BID) or placebo for 12 weeks of delivery. We conducted a post treatment follow up visit 3 months after the last treatment visit. Each week we collected a substance use calendar and urine for cocaine metabolite analysis. Results: The median age for participants was 31 years, 56% were white, 32% black and 12% Hispanic. Retention was at least 80% at each postpartum visit. Participants randomized to progesterone lowered their cocaine use more than did those randomized to placebo (treatment by time  $F=5.41$ ;  $p=.02$ ). The rate of agreement between the 7-day retrospective self-report of cocaine use and urine specimens was 93%. Subjects assigned to progesterone, as compared to placebo, were less likely to submit a urine that was positive for cocaine (treatment wald=11.7,  $p=.003$ ). 41 women were abstinent at baseline and 12 relapsed during the 12 week study period. There was a trend for women who relapsed to be assigned to placebo as compared to progesterone (Wilcoxon Statistic =2.4;  $p=.06$ ). Summary: Progesterone administration to postpartum women with cocaine addiction requires further testing. If the positive results found in this study are replicated in a larger cohort, this may constitute a viable treatment option for postpartum cocaine users.

**Source of Funding:** National Institute for Drug Abuse

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- Sofuoglu M, Babb DA, Hatsukami DK. Effects of progesterone treatment on smoked cocaine response in women. *Pharmacology Biochemistry and Behavior* 2002;72:431.
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#### **DESVENLAFAXINE ER VS PLACEBO IN SOCIAL ANXIETY DISORDER**

*Michael R. Liebowitz<sup>1</sup>, Ester Salman<sup>2</sup>, Ann E. Johnson<sup>3</sup>, Rita Hanover<sup>4</sup>*

*<sup>1</sup>Pherin Pharmaceuticals, <sup>2</sup>WMC Clinical Research Institute, <sup>3</sup>The Medical Research Network, LLC, <sup>4</sup>Westport Compass*

**Purpose:** The purpose of the study was to preliminarily assess the efficacy of desvenlafaxine ER in patients with social anxiety disorder via a placebo controlled trial **Methodology:** Sixty three patients diagnosed with the generalized form of Social Anxiety Disorder (GSAD) per DSM IV

were randomized to desvenlafaxine ER or placebo in a 12 week double blind trial. Change from baseline to endpoint on the Liebowitz Social Anxiety Scale (LSAS) was the primary outcome measure. Secondary outcome measures included response and remission rates and changes in depression and anxiety. Results: The mean baseline LSAS was 92.8 and the mean CGI severity score was 5.4, both indicating severe illness, with no baseline differences between treatment groups. At endpoint, in the ITT sample (N=58), the drug group had improved more than the placebo group by 9.7 points on the LSAS, a trend difference (p=0.085, 1 tailed). There were also trend differences in response rate (69% for drug vs 48.3% for placebo, p=0.09 1 tailed) and remission rate (20.7% for drug vs 3.4% for placebo, p=0.051, 1 tailed), and a significant difference in mean reduction from screening to endpoint on the HAM-D (p=.002, 1 tailed) in favor of desvenlafaxine ER. Importance of the proposed talk: The limited sample size reduced statistical power. However, the findings suggest desvenlafaxine ER may be a promising treatment for Social Anxiety Disorder. As will be discussed, the findings also highlight both the usefulness and the limitations of conducting controlled trials with limited sample sizes.

**Source of Funding:** Investigator initiated grant to The Medical Research Network, LLC from Pfizer

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#### THE PREDICTIVE VALUE OF GENE VARIANTS USED TO GUIDE ANTIDEPRESSANT SELECTION

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**Background** Our previous 10-week prospective, randomized, double-blind pilot study reported a non-significant (p = 0.35) larger percentage (9/25, 36%) of depressed outpatients responded and remitted to antidepressant (AD) treatment guided by a 5-gene (46 gene variants)

pharmacogenomic testing (PGxT) panel compared to treatment as usual (TAU) (5/24, 20.8%).

This post-hoc analysis will characterize the predictive value of the gene variants tested by comparing outcomes predicted by PGx phenotypes to actual clinical outcomes observed with the endpoint AD treatments. **Methods** Data collected during a 10-week PGx study in depressed outpatients and used in this post-hoc analysis included genotype (for gene variants of CYP2D6, CYP2C19, CYP1A2, SLC6A4, and HTR2A), and predicted phenotypes, endpoint AD doses, and treatment outcomes in 25 PGxT (9 remitters/ responders (R/R) and 16 partial responders/failures (PR/F)) and 19 PR/F TAU patients. PGx testing was not performed on 5 R/R TAU patients. R/R was defined as  $\geq 50\%$  decrease and PR/F as  $< 50\%$  decrease in HDRS-17 scores at week 10 from baseline. PGx phenotypes linked to poor or delayed treatment response to affected ADs include: CYP2D6 ultrarapid metabolizer (UM) and CYP1A2 inducible UM, SLC6A4 moderate activity (MA) and low activity (LA). Antidepressant outcomes predicted by PGx phenotypes were compared to actual AD outcomes in study patients. **Results** At study endpoint, 44 patients (19

TAU and 25 PGxT) who underwent PGx testing were treated with a total of 59 antidepressants. The number (%) of patients with phenotypes predicting delayed/poor response to ADs: CYP2D6 UM (n=4 (9%)), CYP1A2 inducible UM (n=17 (38.6%)), SLC6A4 MA (n=19 (43.2%)), and SLC6A4 LA (n=6 (13.6%)). The sensitivity of detecting a poor outcome was 14.3% (5/35), specificity was 100% (9/9), positive predictive value was 100% (5/5), and the negative predictive value was 23.1% (9/39). The accuracy was 31.8% (95% CI: 20.0% - 46.6%). Predictive phenotypes for a poor outcome included CYP2D6 UM (n=1) and SLC6A4 MA or LA (n=4).  
**Conclusions** In this post-hoc analysis of data from our previous study of patients presenting to a large outpatient psychiatric facility for treatment of MDD or depression NOS, we compared antidepressant response as predicted by PGx testing to actual treatment outcomes reported in the study. Overall the PGx testing correctly predicted outcomes in 14/44 (31.8%) of cases. These results highlight the limitations of using PGx testing alone to predict outcomes in depressed outpatients.

### **Learning Objectives:**

- Describe the frequency of selected pharmacogenomic phenotypes in a sample of depressed outpatients.
- Characterize the predictive value of a pharmacogenomic testing panel in a sample of depressed outpatients.

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**Source of Funding:** AssureRx Health, Mason, OH

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## **DETERMINING PHARMACOLOGICAL SELECTIVITY OF THE KAPPA OPIOID RECEPTOR ANTAGONIST LY2456302 USING TRANSLATIONAL RAT TO HUMAN PUPILLOMETRY STUDIES**

*Linda Rorick-Kehn*

*Lilly Research Laboratories, Eli Lilly and Co*

Selective kappa opioid receptor antagonism is a promising experimental strategy for the treatment of depression (1). The kappa opioid receptor (KOR) antagonist, LY2456302, exhibits ~30-fold higher affinity for KOR over mu opioid receptors (MOR), which is the next closest identified pharmacology (2). Here, we determined KOR pharmacological selectivity of LY2456302 by assessing MOR antagonism using translational pupillometry in rats and humans. In rats, morphine-induced mydriasis was completely blocked by the nonselective opioid receptor antagonist naloxone (3 mg/kg, which produced 90% MOR occupancy), while 100 and 300 mg/kg LY2456302 (which produced 56% and 87% MOR occupancy, respectively) only partially blocked morphine-induced mydriasis. In humans, fentanyl-induced miosis was completely blocked by 50 mg naltrexone, while LY2456302 dose-dependently attenuated miosis at 25 and 60 mg (minimal-to-no blockade at 4-10 mg). We demonstrate, for the first time, the use of

translational pupillometry in the context of receptor occupancy to identify a clinical dose of LY2456302 achieving maximal KOR occupancy without evidence of significant mu receptor antagonism.

#### References:

- Harrison C. Opioid receptor blocker shows promise in Phase II depression trial. *Nat Rev Drug Discov.* 2013;12: 415.
- Rorick-Kehn LM, Witkin JM, Statnick MA, et al. LY2456302 is a novel, potent, orally-bioavailable small molecule kappa-selective antagonist with activity in animal models predictive of efficacy in mood and addictive disorders. *Neuropharmacology.* 2014;77C: 131-144.

#### Learning Objectives:

- Discuss data from rodent and human translational studies that were used to determine receptor occupancy levels and pharmacological selectivity of the novel kappa opioid receptor antagonist, LY2456302.
- Provide a model for developing translational biomarkers that have great impact on guiding dose selection in early clinical trials, based upon a clear understanding of target engagement and pharmacological selectivity.

**Source of Funding:** Funding provided by Eli Lilly and Co.

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#### A NATURALISTIC STUDY OF THE CLINICAL UTILITY OF PHARMACOGENETIC TESTING IN PSYCHIATRIC PATIENTS

*Herbert Harris<sup>1</sup>, Rachel Scott<sup>2</sup>, Kathryn Gardner<sup>2</sup>, Jay Lombard<sup>2</sup>, Francis X. Brennan<sup>2</sup>*

*<sup>1</sup>Rho, <sup>2</sup>Genomind*

Study Objective(s): Underlying genetic differences may be an important factor in variable patient responses to psychiatric medications. Therapies informed by a patient's genetic data have the potential to improve outcomes. This study has three major objectives: (1) to demonstrate the efficacy of genetic testing through both patient and clinician reported outcomes, (2) to characterize patient populations selected for pharmacogenetic testing by clinicians, and (3) to demonstrate the impact of genetic testing on clinician treatment decisions. Methods: This is an open label, prospective analysis of assay guided treatment using the Genecept™ assay (Genomind, LLC, Chalfont, PA). Study subjects include patients and their treating clinicians who order the saliva-based gene panel, and all consent and responses are collected electronically. Ten genes are tested for with this assay: the serotonin transporter (SLC6A4), voltage-gated calcium channel (CACNA1C), Ankyrin G protein (ANK3), dopamine receptor subtype two (DRD2), catechol-O-methyl transferase (COMT) and methylenetetrahydrofolate reductase (MTHFR), as well as cytochromes P450 2D6 (CYP2D6), 2C19 (CYP2C19), and 3A4 (CYP3A4). An analytic results report is provided to the clinician and clinical support is available for report interpretation. Clinician subjects are asked to complete a baseline survey prior to receipt of assay results. The clinician baseline survey includes assessment of the patient's current medications, psychiatric history, and severity of illness using the Clinical Global Impressions-Severity (CGI-S) scale. A second survey is completed after results are received, capturing treatment changes guided by the assay. The clinician assesses the patient's improvement at 3



months from the time of genetic testing using the Clinical Global Impressions-Improvement (CGI-I) scale. Patients are asked to complete self-assessments of depression, anxiety, medication side effects, and quality of life at three separate time points (baseline, 1 month, and 3 months). Results: Completed survey data for 659 patients across psychiatric diagnoses has been analyzed. Approximately 60% have a mood disorder and 25% have an anxiety disorder. Seventy three percent of patients were reported to be treatment resistant, having failed two or more adequate medication treatment trials. Clinician-reported CGI-I data indicate 89% of patients show clinically measurable improvement post-Genecept. Strikingly, 90% of the treatment resistant patients also showed clinically measurable improvement. Patient reported data demonstrate significant increases in quality of life, as well as decreases in depression, anxiety, and medication side effects; response rates far exceed those reported in the seminal STAR\*D trial at all levels. Conclusion: The data strongly support the utility of pharmacogenetic testing in improving outcomes in psychiatric patients. Response rates are superior to those seen with standard treatment and are considerably higher than average placebo response rates. Response to psychiatric treatment is highly variable and often involves a number of failed medication trials. Personalized therapies informed by genetic data may ease this burden and improve patient outcomes.

### **Learning Objectives:**

- To understand the utility of genetic testing in treating patients with psychiatric illnesses.
- To understand the characteristics of patients chosen by clinicians to undergo genetic testing.

**Source of Funding:** This study is being funded by Genomind.

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### **HOW CARDINAL ARE CARDINAL SYMPTOMS IN PEDIATRIC BIPOLAR DISORDER? A FAMILIAL RISK ANALYSIS**

*Joseph Biederman<sup>1</sup>, Stephen V. Faraone<sup>2</sup>, Laura M. Tarko<sup>1</sup>, Mariely Hernandez<sup>1</sup>, Janet Wozniak<sup>1</sup>*

<sup>1</sup>Massachusetts General Hospital, <sup>2</sup>SUNY Upstate Medical University

Background: Several investigators have suggested that symptoms of euphoria and grandiosity are cardinal symptoms of pediatric bipolar (BP)-I disorder. If euphoria and grandiosity are truly cardinal symptoms of pediatric bipolar (BP)-I disorder, children with BP-I disorder with these symptoms should have more robust familial rates of BP-I disorder than BP-I disorder children without them. Methods: Patterns of familiarity with BP-I disorder in first degree relatives were compared between pediatric probands (N=232) satisfying DSM-IV criteria for BP-I disorder with and without cardinal symptoms of euphoria and grandiosity. Results: With one exception, ("decreased need for sleep 16% vs. 7%, p=0.0041) patterns of familiarity were indistinguishable in probands with and without individual DSM-IV symptoms of mania (including the symptoms of euphoria and grandiosity) (vs. neither) as assessed with familial risk analysis and logistic regression. Limitations: Because we studied a sample of referred children, our findings may not generalize to community samples. Conclusions: These familial aggregation findings further challenge the notion that euphoria and grandiosity represent cardinal symptoms of mania in children. Instead these findings indicate that all symptoms of mania as defined in the DSM-IV have similar relevance in the diagnosis of pediatric BP-I disorder. They also support the use of unmodified DSM criteria in establishing the diagnosis of mania in pediatric populations.

### **Learning Objectives:**

- The audience will learn that the familiarity of pediatric BP-I disorder is equally robust in children meeting DSM-IV criteria for BP-I disorder with and without euphoria and grandiosity.
- The audience will learn that pediatric bipolar disorder requires similar diagnostic criteria as those used in adult bipolar disorder.

**Source of Funding:** This work was supported by NIMH grants K08 MH0153-03 and R01 MH066237-02 to Dr. Wozniak. This work was also supported by the MGH Pediatric Psychopharmacology Council Fund.

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### **HIGH EPA OMEGA-3 FATTY ACIDS AND INOSITOL AS MONOTHERAPY AND IN COMBINATION IN THE TREATMENT OF PEDIATRIC BIPOLAR DISORDER: A PILOT DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL**

*Joseph Biederman<sup>1</sup>, Stephen V. Faraone<sup>2</sup>, Laura M. Tarko<sup>1</sup>, Mariely Hernandez<sup>1</sup>, Janet Wozniak<sup>1</sup>*

*<sup>1</sup>Massachusetts General Hospital, <sup>2</sup>SUNY Upstate Medical University*

**Objectives:** We conducted a randomized, double-blind, controlled clinical trial to evaluate the effectiveness and tolerability of high EPA/DHA omega-3 fatty acids and inositol as monotherapy and in combination in children with bipolar and bipolar spectrum disorder. **Methods:** Participants were children 6-12 years of age meeting DSM-IV diagnostic criteria for bipolar spectrum disorder (bipolar disorder- I, II, or Not Otherwise Specified (NOS)), and displaying mixed, manic, or hypomanic symptoms. Subjects were randomized in double-blind fashion to one of three treatment arms: high EPA/DHA omega-3 fatty acids (3000 mg and placebo, inositol (for subjects  $\geq 25$ kg 2000mg, and those  $< 25$ kg at 80mg per kg) and placebo, and the combined active treatment of omega-3 fatty acids and inositol. **Results:** N=24 were exposed to treatment ( $\geq 1$  week of study completed) (N=7 to Inositol, N=7 to omega-3 fatty acids, and N=10 to the combined treatment (both omega-3 fatty acids and inositol). Subjects randomized to the combined treatment of omega-3 fatty acids and inositol showed significantly greater improvement on the YMRS than those treated with inositol ( $p=0.021$ ) and omega-3 fatty acids ( $p=0.046$ ) alone. The combined treatment also had the largest effect size comparing improvement from baseline to endpoint with respect to the YMRS ( $p<0.001$ ). Subjects randomized to the combined treatment also showed significantly greater improvement in symptoms of depression on the Hamilton Rating Scale for Depression (HAM-D) than either inositol ( $p=0.021$ ) or omega-3 fatty acids ( $p=0.046$ ) alone ( $p=0.001$  and  $p=0.048$ , respectively). The combined treatment also had the largest effect size comparing improvement from baseline to endpoint of the study with respect to the HAM-D scale ( $p<0.001$ ). The most commonly reported adverse event was gastrointestinal problems (reported  $\geq 2$  times:  $n=0$  for inositol,  $n=3$  for omega-3 fatty acids, and  $n=2$  for omega-3 fatty acids and inositol combined). **Conclusions:** Results of this pilot randomized, double-blind, controlled trial showed that the combined treatment of omega-3 fatty acids and inositol reduced symptoms of mania and depression in pre-pubertal children with bipolar spectrum disorders and were very well tolerated.

### **Learning Objectives:**

- The audience will learn about the effectiveness of omega-3 fatty acids and inositol as monotherapy and in combination, in the treatment of pediatric bipolar disorder.
- The audience will learn about the excellent tolerability of omega-3 fatty acids and inositol as monotherapy and in combination, in the treatment of pediatric bipolar disorder.

**Source of Funding:** This work was supported by the MGH Pediatric Psychopharmacology Council Fund.

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## **IDENTIFYING PATIENTS MEETING THE DSM-5 CRITERIA FOR BIPOLAR DISORDER EPISODES WITH MIXED FEATURES IN BIPOLAR DISORDER STUDIES WITH QUETIAPINE XR**

*Catherine Datto, Jason Wright, Scott LaPorte, Michelle Shay*

*AstraZeneca*

Introduction: The DSM-5 has introduced the “mixed features” specifier in acute bipolar disorder episodes. The rationale for the use of this specifier in acute depressive or manic episodes is to detail the presence of symptoms of the opposite pole. Methods: This analysis applied the DSM-5 criteria post hoc to randomized controlled clinical trials of quetiapine extended release (XR) in patients with DSM-IV-TR defined acute depressive episodes of bipolar I or II disorder (1) or acute manic or mixed episodes of bipolar I disorder.(2) As these studies captured standardized assessments for symptoms of the identified episode and the opposite pole, such application of the new DSM-5 criteria was possible. Results: 280 patients were randomized in the bipolar depression (including bipolar I or II) study. Of these, 78 patients were identified post hoc as meeting DSM-5 criteria for mixed features. At the end of the 8-week course of treatment in the full study population, quetiapine XR patients in the modified intent-to-treat (MITT) population had a least squares (LS) mean decrease in MADRS total score 5.5 points greater than placebo-treated patients ( $P<0.001$ ). At Week 8 in the mixed features subgroup, the quetiapine XR group had a LS mean decrease in MADRS score 3.63 points greater than in the placebo group ( $P=0.099$ ). 313 patients were randomized in the bipolar I mania study. Of these, 145 patients were identified post hoc as meeting DSM-5 criteria for mixed features. In the full bipolar mania population at Week 3, the quetiapine XR group in the MITT population had a LS mean decrease in YMRS score 3.83 points greater than patients in the placebo group ( $P<0.001$ ). At Week 3 in the mixed features subgroup, the quetiapine XR group had a LS mean decrease in YMRS score 2.12 points greater than in the placebo group ( $P=0.11$ ). Quetiapine XR when used as monotherapy in patients with acute bipolar I or II depression and bipolar I mania was generally well tolerated. Conclusion: Applying the DSM-5 criteria for mixed features in patients with acute depressive episodes of bipolar I or II disorder as well as acute manic episodes of bipolar I disorder has identified small subgroups of patients in randomized acute trials of quetiapine XR. In the setting of these small numbers, there was numerical (non-statistically significant) improvement in patients treated with quetiapine XR over placebo. Treatment considerations for patients meeting these mixed features criteria warrant further attention. Literature References 1. Suppes T, Datto C, Minkwitz M, et al. J Affect Disord. 2010;121:106-15. 2. Cutler AJ, Datto C, Nordenhem A, et al. Clin Ther. 2011;33:1643-58.

### **Learning Objectives:**

- At the conclusion of this presentation, the participant should be able to demonstrate knowledge and understanding of the DSM-5 criteria for mixed features and application of these criteria to randomized controlled trials using quetiapine XR.
- At the conclusion of this presentation, the participant should learn about the DSM-5 new modifiers for use in bipolar disorder diagnoses.

**Source of Funding:** AstraZeneca

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## **LURASIDONE MONOTHERAPY FOR BIPOLAR DEPRESSION: INFLUENCE OF BASELINE THYROID FUNCTION ON TREATMENT RESPONSE**

*Joseph F. Goldberg<sup>1</sup>, Andrei Pikalov<sup>2</sup>, Kei Watabe<sup>2</sup>, Antony Loebel<sup>2</sup>*

*<sup>1</sup>Icahn School of Medicine at Mount Sinai, <sup>2</sup>Sunovion Pharmaceuticals, Inc.*

Introduction: Response of patients with bipolar depression to treatment with lithium and antidepressant therapy has been reported to be sensitive to baseline thyroid status, with poorer response observed in patients with lower free thyroxine index values and higher TSH values, even within normal reference ranges (1, 2). This post-hoc analysis (3) evaluated whether thyroid function level influenced treatment response to lurasidone in patients diagnosed with bipolar I depression. Methods: Patients meeting criteria for bipolar I depression, with a MADRS score  $\geq 20$ , were randomized to 6 weeks of once-daily, double-blind treatment with either lurasidone 20-60 mg, lurasidone 80-120 mg (combined in the current analysis, n=323) or placebo (n=162). Patients receiving ongoing thyroid hormone treatment (n=27) were excluded from the analysis. Baseline levels of thyroid-stimulating hormone (TSH; normal reference range, 0.35-1.8  $\mu\text{IU/mL}$ ) and free thyroxine (free T4; normal reference range, 0.35-5.5 ng/dl) were obtained at screening. Patients were first stratified by median split in baseline TSH (high-normal TSH group, lurasidone n=159; placebo, n=81; and a low-normal TSH group, lurasidone n=159; placebo, n=79), and then further stratified into 1 of 4 baseline thyroid function categories based on a median split of high-normal vs. low-normal free T4. Efficacy was assessed as change in MADRS from baseline to week 6 (LOCF, ANCOVA). Results: At baseline, the median TSH was 1.6  $\mu\text{IU/mL}$ , the median free T4 was 1.01 ng/dl, and the mean MADRS was 30.5. LS mean change from baseline in MADRS was significant for lurasidone vs. placebo in both the high-normal and low-normal TSH groups. The proportion of patients meeting endpoint responder criteria ( $\geq 50\%$  reduction in MADRS) was also significantly higher for lurasidone vs. placebo in both the high-normal TSH group (54.5% vs. 36.7%;  $p < 0.05$ ) and the low-normal TSH group (49.0% vs. 26.7%;  $p < 0.01$ ). Based on a further stratification by median free T4 values, patients with lower baseline thyroid function (high-normal TSH + low-normal free T4) had greater effect sizes (0.43 vs. 0.20) for improvement in MADRS with lurasidone than patients with higher baseline thyroid function (low-normal TSH + high-normal T4). Conclusions: Lurasidone was effective in treating patients with bipolar depression who had thyroid function within the clinical reference range. In contrast to previous reports in the literature (1, 2), response to lurasidone was not lower in patients with low-normal FT4 and high-normal TSH. Further research is needed to evaluate whether these findings extend to patients with clinically significant thyroid abnormalities, and to determine whether the optimal dose of lurasidone may be influenced by baseline thyroid status.

## **References:**

- Cole DP, Thase ME, Mallinger AG et al. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. *Am J Psychiatry* 2002;159:116-21.

- Chakrabarti J. Thyroid functions and bipolar affective disorder. *Thyroid Res* 2011;1-13.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone Monotherapy in the Treatment of Bipolar I Depression. *Am J Psychiatry* 2014;171:160-168.

#### **Learning Objectives:**

- At the completion of this session participants will be able to demonstrate knowledge of the safety and tolerability of lurasidone in the short-term treatment of bipolar depression.
- At the completion of this session participants will be able to demonstrate knowledge of the effect of baseline thyroid function status on treatment response to lurasidone in patients with bipolar depression.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals Inc.

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### **SCREENING AND VALIDATION OF NOVEL KINASE SIGNALING PATHWAYS FOR NEURONAL EXCITABILITY**

*Wei-Chun Hsu<sup>1</sup>, Miroslav Nenov<sup>2</sup>, Alexander Shavkunov<sup>2</sup>, Neli Panova-Elektronova<sup>2</sup>, Fernanda Laezza<sup>3</sup>*

<sup>1</sup>*University of Texas Medical Branch at Galveston,* <sup>2</sup>*The University of Texas Medical Branch,* <sup>3</sup>*Pharmacology*

Brain disorders are complex, multifactorial diseases characterized by disruption of neural circuits, leading to impairments in neural plasticity and excitability. Though studies of brain disorders reveal that impaired signaling pathways lead to dysregulation of neuronal excitability, synaptic plasticity and brain connectivity, there is a need to interrogate the signaling pathways that underlie the pathogenesis and manifestation of brain disorders. To discover new signaling pathways that regulate neuronal excitability, we have performed a high-throughput screening of kinase inhibitors against the FGF14-Nav1.6 complex, a protein complex critical for neuronal excitability located at the axonal initial segment. We demonstrate through a protein-fragment complementation assay over a dozen inhibitors that significantly alter the FGF14-Nav1.6 complementation, and have identified an Akt/GSK-3/Wee1 regulatory network that may modulate neuronal excitability. Through high-content confocal imaging and electrophysiology, we aim to demonstrate the spatial distribution of cellular components and the functional consequences of signaling pathway modulation, to understand the consequences of dysregulated excitability in brain disorders. Positive outcomes of this study will provide new knowledge of the molecular basis of brain disorders.

#### **Learning Objectives:**

- To identify new signaling pathways that may influence neuronal excitability, which is dysregulated in disorders such as schizophrenia and bipolar disorder
- To investigate new methodologies for validating the biochemical, cellular, and functional effects of perturbing these signaling pathways.

**Source of Funding:** National Institutes of Health Grant MH095995 from NIMH (FL) Clinical and Translational Science Award UL1TR000071 from NCATS (FL) PhRMA Foundation (FL)

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## **MEDIATORS OF EFFECTS OF LURASIDONE ON FUNCTIONING AND QUALITY OF LIFE: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN PATIENTS WITH BIPOLAR I DEPRESSION**

*Terence Ketter<sup>1</sup>, Cynthia Siu<sup>2</sup>, Krithika Rajagopalan<sup>3</sup>, Andrei Pikalov<sup>3</sup>, Antony Loebel<sup>3</sup>*

*<sup>1</sup>Stanford University School of Medicine, <sup>2</sup>Data Power, <sup>3</sup>Sunovion Pharmaceuticals, Inc.*

**Objectives:** The objective of this post-hoc analysis was to evaluate the effect of lurasidone on quality of life in patients with bipolar I depression. Relationships between treatment-related reductions in depressive symptoms, functional improvement, and quality of life were also assessed. **Methods:** Subjects meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, were randomized to 6 weeks of once-daily, double-blind treatment with either lurasidone 20-60 mg, lurasidone 80-120 mg or placebo. The primary efficacy endpoint was the mean change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. Functional remission criteria were met when subjects attained mean Sheehan Disability Scale (SDS) total score  $\leq 3$  and all SDS domain scores  $\leq 2$ . Quality of life was assessed using the Quality of Life and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF). Mediation analysis (involving a series of regression models) was applied. **Results:** Lurasidone treatment significantly reduced mean MADRS total scores at week 6 for both the 20–60 mg/day group (-13.9, SD 9.81;  $P < 0.001$ ) and 80–120 mg/day group (-13.9, SD 9.81;  $P < 0.001$ ), compared with placebo (-9.5, SD 9.81). Similarly, lurasidone treatment resulted in significantly greater improvement in SDS total scores for both the 20–60 mg/day group (-9.5, SD 7.0;  $P = 0.003$ ) and the 80–120 mg/day group (-9.8, SD 7.0;  $P < 0.001$ ) compared with placebo (-6.3, SD 7.0) at week 6, as well as Q-LES-Q total scores for both the 20–60 mg/day group (19.3, SD 16.5;  $P < 0.001$ ) and the 80–120 mg/day group (19.8, SD 16.5;  $P < 0.001$ ) compared with placebo (12.8, SD 16.5) at week 6. A significantly higher proportion of subjects treated with lurasidone 20–60 mg/day (33%) or 80–120 mg/day (34%) attained functional (SDS) remission compared with placebo (22%) at week 6 ( $P < 0.05$ ). Mediation regression analysis showed that reduced depressive symptoms from baseline to week 6 mediated the effect of lurasidone (vs. placebo) on functional remission and Q-LES-Q improvement at week 6 (all  $P < 0.05$ ). Functional remission was associated with a higher likelihood of improved quality of life ( $P < 0.05$ ). **Conclusions:** Monotherapy with lurasidone in the dosage range of 20–120 mg/day significantly reduced depressive symptoms, and improved functioning and quality of life in patients with bipolar I depression. Reduced depressive symptoms mediated the effects of lurasidone (vs. placebo) on functioning and quality of life.

### **Learning Objectives:**

- To understand the effect of lurasidone on quality of life in bipolar I depression.
- To understand the relationships between treatment-related reductions in depressive symptoms, functional remission, and quality of life in bipolar I depression.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals Inc.

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## **PREDICTORS OF IMPROVEMENT IN QUALITY OF LIFE ASSOCIATED WITH LURASIDONE TREATMENT OF BIPOLAR I DEPRESSION: RESULTS FROM A 6-MONTH CONTINUATION STUDY**

*Terence Ketter<sup>1</sup>, Cynthia Siu<sup>2</sup>, Mariam Hassan<sup>3</sup>, Krithika Rajagopalan<sup>3</sup>, Andrei Pikalov<sup>3</sup>, Antony Loebel<sup>3</sup>*

<sup>1</sup>Stanford University School of Medicine, <sup>2</sup>Data Power, <sup>3</sup>Sunovion Pharmaceuticals, Inc.

**Objectives:** Recovery in bipolar depression requires remission of clinical symptoms as well as improved functioning and quality of life. The objective of this post-hoc analysis was to investigate predictors of improvement in quality of life in patients with bipolar I depression treated with lurasidone for up to 6 months after completion of a short-term, placebo-controlled acute study. **Methods:** Subjects meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, were randomized to 6 weeks of once-daily, double-blind treatment with either lurasidone 20-60 mg, lurasidone 80-120 mg or placebo. A total of 318 intent-to-treat subjects enrolled in the 6-month, open-label, continuation study of lurasidone. Subjects initially treated with placebo were started on flexible once-daily doses of lurasidone 40-160 mg/d (N=107). Quality of life was assessed using the Quality of Life and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), a 16-item self-report (using a computer interface) measure of the degree of enjoyment and satisfaction in various domains of daily living. We developed a multivariate logistic regression model to predict the likelihood of achieving 50% or greater improvement in Q-LES-Q-SF total score from acute study baseline, and to quantify the relationship of patient characteristics and week-6 treatment outcomes on improving patient's quality of life in the 6-month continuation study. **Results:** During up to 6 months of lurasidone continuation treatment, 143 (53%) demonstrated a 50% or greater improvement in Q-LES-Q-SF total score from acute study baseline. Reduction of depressive symptoms at week 6 increased the likelihood of achieving an at least 50% improvement in quality of life total score at 6-month follow-up ( $p<0.05$ ). Lower mood disorder severity at acute study baseline (as assessed by Clinical Global Impression Bipolar Version, Severity of Illness), less chronically ill, race (non-white population including 13% Black or African Americans, 12% Asian, 7% other), and lower Q-LES-Q-SF total score were significant baseline predictors of quality of life improvement at month 6. Greater impairment in functioning as assessed by higher Sheehan Disability Scale mean score at week 6 also significantly predicted lower likelihood of quality of life improvement, but was not independent of reduction in depressive symptoms at week 6. A multivariate function based on these baseline clinical and early response predictors showed statistically acceptable calibration performances based on c-statistics (AUC ROC=0.81). Gender was not a significant predictor for quality of life improvement ( $P>0.05$ ). **Conclusions:** Lurasidone was associated with significant improvement in quality of life. Our findings suggest that a parsimonious model incorporating early improvement in depressive symptoms and baseline clinical status can be developed for predicting patients' likelihood of achieving favorable, long-term quality of life outcomes.

### **Learning Objectives:**

- To understand predictors of improvement in quality of life associated with lurasidone treatment of bipolar I depression.
- To understand the relationship between initial response to lurasidone treatment of bipolar I depression and improvement in quality of life in a 6-month continuation study.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals Inc.

*Jamie Mullen, Catherine Datto, Louisa Feeley, Scott LaPorte  
AstraZeneca*

**Introduction:** Although the exact prevalence rate of bipolar II disorder is uncertain, it is at least as prevalent as bipolar I. (1) However, it is often misdiagnosed and undertreated, and can be associated with significant disability and comorbidity. (2) **Methods:** To compare the severity and burden of illness between patients with bipolar I and II disorder, we examined the clinical, demographic, and quality of life baseline data from 1900 patients with bipolar I and 973 with bipolar II disorder enrolled in 5 bipolar depression clinical trials of quetiapine immediate-release and quetiapine extended-release formulations. The diagnosis of bipolar I or II disorder was confirmed using the Structured Clinical Interview for DSM-IV (SCID). **Results:** Bipolar I and bipolar II populations had similar proportions of females (58.8% and 62.7%) and similar mean age (39.5 and 38.7 years, respectively), but patients with bipolar I had a numerically higher mean weight (83.3 vs 79.7 kg) than those with bipolar II. Other baseline characteristics were similar between these groups. Patients with bipolar I and II disorder had similar mean baseline MADRS (29.4 vs 27.8, respectively), HAM-D (22.1 vs 23.0), YMRS (5.3 vs 4.8), CGI-BP-S (4.4 vs 4.3), and HAM-A scores (18.3 vs 19.0). Patients with bipolar I and II disorder also had similar mood episode histories: lifetime depressive episodes (13.0 vs 13.0), last-year depressive episodes (1.4 vs 1.4), lifetime manic or hypomanic episodes (9.7 vs 9.8), and last-year manic or hypomanic episodes (1.0 vs 1.0). In addition, patients with bipolar I and II disorder had similar quality of life as measured by Q-LES-Q score (36.2 vs 36.7). **Conclusion:** Historically, bipolar II was thought to be less disabling than bipolar I disorder. In this analysis of patients enrolled in treatment trials of bipolar depression, however, bipolar II patients had a similar burden of illness and quality of life. Since treatment approaches may differ for bipolar I and II disorders, and clinical features at the time of depressive episodes did not differentiate these 2 disorders, a careful inquiry into episodes suspicious for mania or hypomania is important to distinguish between these 2 disorders.

#### **References:**

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- Hadjipavlou G, Mok H, Yatham L. Can J Psychiatry. 2004;49:802-812.

#### **Learning Objectives:**

- At the conclusion of this presentation, the participant should understand the severity and burden of illness in patients with bipolar I disorder.
- At the conclusion of this presentation, the participant should understand how severity and burden of illness compare in patients with bipolar I disorder to patients with bipolar II disorder.

**Source of Funding:** AstraZeneca

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#### **NEURAL CORRELATES OF SOCIAL STRESS IN YOUTH WITH BIPOLAR DISORDER**

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**Objective/Hypothesis:** To examine the neural correlates of social stress in youth with bipolar disorder (BD). We examined brain activation and connectivity in youth with BD undergoing an fMRI acute social stress task and correlated brain activation to behavioral symptom severity.

**Methods:** **Participants:** fMRI scans were conducted on 13 youth ages 10-17 years old (mean 15.1 +/- 1.8 years) diagnosed with BD per DSM-IV TR criteria and 16 age- (mean 14.7 +/- 2.3 years) and gender-matched HC on a 3T General Electric MR750 scanner (General Electric; Milwaukee). **fMRI Imaging Protocol:** Participants were scanned while playing Cyberball, a ball tossing computer game used to study the effects of social rejection. They were included during the first game and then excluded during the second. Subjects were assessed for anxiety and anger symptoms of rejection sensitivity and for the severity of distress felt after the social rejection task. **fMRI Analysis:** Data preprocessing, individual voxel-wise statistics, and individual voxel-wise t-maps were performed in SPM8, for the contrast of exclusion minus inclusion. Whole-brain voxelwise analyses were conducted in SPM8, using a two-sample t-test. Within the BD group, Dynamic Causal Modelling was used to explore effective connectivity of a priori regions and determine the posterior probability that these connections modulated the effect of exclusion. Spearman's correlation was used to examine the association between mean activation levels in the amygdala, anterior insula (AI), and ventrolateral prefrontal cortex (VLPFC), with severity of rejection sensitivity and distress after the task, corrected for multiple comparisons by False Discovery Rate (FDR). **Results:** Significant group differences were found in activation of the left AI, left amygdala, subgenual anterior cingulate cortex (sgACC), rostral extent of the dorsal anterior cingulate cortex (dACC), and VLPFC. Within the BD group, amygdala modulation of AI was shown to have a higher posterior mean probability ( $P(B)=0.6$ ) than either VLPFC modulation of amygdala ( $P(B)=0.5$ ) or of anterior insula ( $P(B)=0.5$ ). Within the BD group only, there was a trend for significance for less VLPFC activation associated with greater severity in both the anxiety domain ( $p=.093$ ,  $\rho=-0.62$ , FDR corrected) and anger domain ( $p=.093$ ,  $\rho=-0.63$ , FDR corrected) of rejection sensitivity. **Conclusions:** In addition to anterior insula, sgACC, rostral area of the dACC, and VLPFC, areas previously associated with social rejection, youth with BD also significantly activate the amygdala when compared with HC, suggesting greater fear and anxiety when faced with social evaluation and rejection. Greater connectivity of amygdala to AI than VLPFC to AI may imply aberrant circuitry in the regulation of AI in the BD group. Less activation of VLPFC with greater rejection sensitivity symptom severity in the BD group may suggest greater VLPFC difficulties in regulating areas activated in social rejection. To our knowledge, no other published studies exist associating neural correlates to social stress in youth with BD. This study provides biological markers of response to future proposed treatments to reduce social stress and thereby improve symptoms and functioning in this population highly vulnerable to suicide and psychiatric comorbidities.

### **Learning Objectives:**

- Participants will understand the role and importance of social stress in the development of bipolar disorder in youth.
- Participants will be able to identify the differences in brain activation and circuitry in social stress in youth with bipolar disorder vs. healthy controls.

**Source of Funding:** American Academy of Child and Adolescent Psychiatry/Lilly Pilot Research Award

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## **THE YOUNG MANIA RATING SCALE IN BIPOLAR DISORDER: EVALUATION OF SLEEP AND RATER TRAINING**

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*<sup>1</sup>Rater Training Services at inVentiv Health Clinical, <sup>2</sup>inVentiv Health Clinical, <sup>3</sup>inVentiv Health*

**Introduction:** The Young Mania Rating Scale (YMRS) is the scale most frequently used as primary measure of mania in clinical trials of Bipolar Disorder (BD). Rater Training Programs aim to maintain rating standardization and improve raters' assessment skills, relying on ratings accuracy to document a positive drug effect. Raters' competency on the YMRS is especially relevant as certain items are particularly complex, leading to less accurate ratings and increased inter-rater variability. **Method:** In the context of a phase III clinical trial of Bipolar Disorder I Mania with the YMRS used as primary efficacy measure, 20 raters from Russia, Poland, Spain, Italy, Turkey, Austria and Greece who had limited clinical/rating experience were required to complete a co-rating program as requisite for their qualification in the study, which included: • Watch a didactic presentation on the YMRS • Watch a videotaped YMRS interview followed by feedback information about the expected scores. • Assess 5 bipolar patients using the YMRS under the supervision of an experienced rater. Provide ratings and rationales for each patient/item to the inVentiv Health Clinical Rater Training Services (RTS) team and receive feedback about their ratings. Raters were asked for clarifications or received additional training when they had missed any rating, provided inconsistent rationales, or when there was poor evidence of the information obtained for each item assessment. **Results:** We identified 5 items of the YMRS that most consistently required feedback and re-training: Sleep, Irritability, Disruptive-Aggressive Behaviors, Thought Content and Speech-Rate and Amount. On the other hand, Appearance and Insight showed more accurate ratings and less need for feedback. These findings are consistent with the reported higher rating difficulty of the YMRS items with severity graded on a 0 - 8 scale. However, the item where non experienced raters needed more intervention in this co-rating program was Sleep, which is not among those typically identified as being particularly difficult to rate in the YMRS. **Discussion:** Sleep disturbance is recognized as an essential aspect of affective illnesses and a target in the management of BD. Decreased sleep has been found to be a significant predictor of the onset of a manic episode in BD patients, and teaching patients to recognize early symptoms and seek treatment is associated with an increased time to a manic episode and an improvement in occupational and social functioning. Given the crucial role that sleep and its disturbances play in BD, appropriate evaluation of the different possible signs of sleep disturbance is fundamental. Raters participating in BD clinical trials that use YMRS as efficacy measure should receive detailed training on the items identified as being more difficult to rate or leading to more variability, including Item 4-Sleep, particularly for less experienced raters.

### **Learning Objectives:**

- To show which YMRS items are most prone to errors by the raters.
- To highlight the importance of appropriate rater training of the YMRS items that are target in the management of patients with BD.

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## **FACTORS INFLUENCING THE DIAGNOSIS AND TREATMENT OF BIPOLAR DEPRESSION: A HEALTHCARE PROFESSIONAL PERSPECTIVE**

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*<sup>1</sup>Sunovion Pharmaceuticals, Inc., <sup>2</sup>Harvard Medical School, <sup>3</sup>Health and Wellness Partners*

**Background:** Accurate diagnosis and appropriate treatment of bipolar depression can be challenging, in part because the established diagnostic criteria for a major depressive episode are identical for episodes associated with bipolar disorder and for those associated with major depressive disorder.<sup>1,2</sup> Diagnosis and treatment of bipolar depression are further influenced by prescriber attitudes, knowledge, and practice behaviors. **Objective:** To describe real-world practice patterns related to diagnosis and treatment for patients with bipolar depression.

**Methods:** During an educational meeting on the treatment of bipolar depression, 281 healthcare professionals (HCPs) were surveyed about the proportion of patients with bipolar disorder in their practice, timing of diagnosis, comorbidities/conditions that may mask bipolar disorder, use of adjunctive therapy versus monotherapy, and of the effect of adjunctive antidepressants in the treatment of bipolar disorder. **Key Findings:** Survey respondents were primarily psychiatrists (89%) who practice in the outpatient setting (81%). Most respondents (79%) reported that  $\geq 15\%$  of their total patient pool had been diagnosed with bipolar disorder, and they identified unipolar depression as the most common misdiagnosis of patients later diagnosed with bipolar disorder. The largest proportion of respondents (76%) indicated that their patients with bipolar disorder spend  $>51\%$  of their symptomatic time in the depressed phase. They reported substance abuse and anxiety disorders to be the most common comorbidities among patients with bipolar disorder. Nearly half of the respondents indicated that  $>25\%$  of their patients with bipolar disorder also had metabolic syndrome. Fifty-four percent of respondents indicated that  $>16\%$  of patients being diagnosed with bipolar depression had previously never been diagnosed with any psychiatric disorder. Respondents reported that the majority of patients with bipolar depression are seldom managed with any medication as monotherapy. Sixty-four percent of respondents reported that  $>40\%$  of patients being treated for bipolar disorder with lithium and/or valproate require a change in medication due to a breakthrough depressive episode. More than half of the respondents (56%) indicated limited, if any, awareness of clinical trial data showing lack of efficacy of adding antidepressants to mood stabilizers in the treatment of bipolar depression. **Conclusions:** A survey of HCPs highlights some factors that impact real world diagnosis and treatment of bipolar depression. These findings suggest a need to educate HCPs about best practices in identifying bipolar depression and determining the appropriate treatment course.

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- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC, American Psychiatric Association, 2013.
- Phillips ML, Kupfer DJ: Bipolar disorder diagnosis: challenges and future directions. *Lancet* 2013; 381:1663–1671.

### **Learning Objectives:**

- Describe practice behaviors that complicate the diagnosis of bipolar depression.
- Discuss real-world practice patterns influencing treatment planning and health outcomes for patients with bipolar depression.

## SEQUENCE ANALYSIS OF DRUG TARGET GENES WITH SUICIDE SEVERITY IN BIPOLAR DISORDER

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A number of novel candidate genes have been identified in recent genome-wide association studies of suicide attempt in bipolar disorder. However, the historical candidate genes, including NTRK2, HTR1A, and HTR1B, did not appear to be among the top findings in these studies. Perhaps a combination of rare and common variants may contribute to the predisposition to suicidal behavior. We analyzed 3199 DNA variants across 202 drug target genes (Nelson et al, Science 2012) in our sample of bipolar disorder patients of European ancestry. We analyzed the phenotype of suicide severity score (from the Schedule for Clinical Assessment in Neuropsychiatry SCAN: 0=non-suicidal; 1=suicide plan/ideation; 2=suicide attempt without serious harm; 3=suicide attempt with serious harm; 4=suicide attempt designed to end life; N=227). We conducted preliminary analysis, including individual variant tests using PLINK, and gene-based test using GRANVIL, including history of alcohol use disorder, sex, and age as covariates. Among the findings, we found a number of DNA variants in TGFBR1 to be nominally associated with suicide severity scores ( $p < 0.05$ ). The gene-based tests also pointed to TGFBR1 to be associated with suicide severity ( $p < 0.0001$ ). Conclusions: We analyzed high-throughput targeted sequence data with suicide severity in bipolar disorder and found a number of gene regions to be possibly associated with suicidality, including TGFBR1. We will be incorporating functional annotation in further analysis of this data. The top findings will be validated by Sanger sequencing or SNP genotyping. We will attempt to replicate the validated results in other bipolar and psychiatric disorder samples.

### Learning Objectives:

- To learn the latest trends in translating research findings to drug development.
- To present at the meeting and gain feedback from experts in the field of psychopharmacology.

**Source of Funding:** American Foundation for Suicide Prevention, Eli Lilly Canada, Brain and Behavior Research Foundation

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## IMMUNOLOGICAL STRESS RESPONSIVITY AS A POTENTIAL RISK FACTOR IN PEDIATRIC MOOD DISORDERS

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Background: Youth with mood disorders such as bipolar disorder (BD) or major depressive disorder (MDD) may have unique reactivity to psychosocial stressors, which may in turn alter patterns of cytokine secretion. In this study, we investigated how cytokine reactivity shifts in response to a laboratory stress test in youth with mood disorders compared with healthy controls. Methods: Participants were recruited from the Pediatric Bipolar Disorders Research Program at Stanford University. Participants with BD met DSM criteria for BD I or II. Youth at high risk for BD (MDD) had a parent with a diagnosis of BD I or II and met DSM criteria for MDD. Healthy

controls (HC) and their biological parents were free of any psychiatric diagnosis. Youth completed a Trier Social Stress Test (TSST), a laboratory psychosocial stress test that induces “real-world” stress in a standardized setting. Peripheral levels of cytokines including Interleukin (IL)-6, Tumor Necrosis Factor alpha (TNF- $\alpha$ ), IL-10, and Interferon gamma (IFN $\gamma$ ) were measured before onset of the stressor and then at 30, 60, and 90 minutes. Multivariate profile analysis was used to evaluate cytokine stress responsivity during the TSST. Results: Participants ( $n = 51$ ) were  $14.42 \pm 2.1$  years old and 51% male. Pre-stressor cytokine levels did not differ between BD, MDD, and HC groups for IL-6 ( $F=1.04$ ,  $p=.36$ ), TNF- $\alpha$  ( $F=.90$ ,  $p=.42$ ), IL-10 ( $F=.18$ ,  $p=.83$ ), or IFN $\gamma$  ( $F=1.73$ ,  $p=.19$ ). For IL-6 ( $F=6.44$ ,  $p<.01$ ), TNF- $\alpha$  ( $F=3.8$ ,  $p=.02$ ), IL-10 ( $F=2.93$ ,  $p=.04$ ), and IFN $\gamma$  ( $F=3.22$ ,  $p=.03$ ), there was a main effect for cytokine such that all reliably increased with a linear trend in response to stress. There was a trend for differences between groups for TNF- $\alpha$  ( $p=.17$ ) and IFN $\gamma$  ( $p=.15$ ) such that the HC group experienced greater cytokine increases than did BD or MDD groups. Conclusions: Healthy youth may respond differently from youth with mood disorders to acute psychological stress. This study begins to deconstruct the complex interplay between inflammation and response to stress which may be a factor in the development of mood disorders in vulnerable populations.

#### **Learning Objectives:**

- To present findings from a laboratory-based study examining immune response to stress in youth with mood psychopathology.
- To explore the relationship between the immune system and the etiology of mood psychopathology in youth.

**Source of Funding:** Pilot Early Career Grant from Spectrum Child Health at Lucille Packard Children's Hospital (PI: V. Cosgrove)

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#### **INTER-RATER RELIABILITY OF THE SCALES FOR OUTCOMES OF PARKINSON'S DISEASE – COGNITION (SCOPA-COG) IN MODERATO: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO ASSESS THE EFFECT OF RASAGILINE ON MILD COGNITIVE IMPAIRMENT IN PD PATIENTS**

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<sup>1</sup>INC Research, <sup>2</sup>Teva Pharmaceuticals

**Background:** The SCOPA-COG was developed for use in clinical research and has demonstrated good internal consistency, test-retest reliability, and construct validity. However, inter-rater reliability of the SCOPA-COG is unknown, which is a notable gap in the research because of its increasing use in multi-center clinical trials. The purpose of the present study was to examine inter-rater reliability and to provide detailed analyses of administration and scoring errors.

**Method:** The MODERATO study is a multi-center, randomized, placebo-controlled trial examining the effect of rasagiline on cognition in patients with PD. The SCOPA-COG, which consists of 10 items that comprise four subscales (i.e., Memory, Attention, Executive Functions, and Visuospatial Functions), is the primary endpoint. In an effort to maximize inter-rater reliability, a robust training program was employed consisting of (1) on-line didactic and video training requiring perfect scores on post-assessment and (2) videotaped administrations to mock patients requiring a certification video without “major” errors (defined as errors clearly affecting the subject's score), which were determined by calibrated expert raters who reviewed each videotaped administration and provided corrective feedback. Following successful completion of

SCOPA-COG training, raters were certified to begin testing study subjects. During the trial, each study subject's SCOPA-COG was videotaped and reviewed by an expert rater who was blinded to the scores given by the site rater. The expert rater independently scored the assessment, and inter-rater reliabilities for expert rater and site rater scores were calculated for the total score, subscales, and individual items. In addition, inter-rater reliabilities for site raters who had performed multiple assessments were computed to explore the impact of experience and corrective feedback over time. Finally, detailed analyses of the types of errors affecting subjects' scores were conducted. Results: At the time of submission, 25 site raters had conducted 88 videotaped SCOPA-COG administrations, which had been reviewed by two expert raters. Nineteen of the site raters had performed at least two SCOPA-COG subject administrations. The overall inter-rater reliability for the SCOPA-COG total score was .98, and inter-rater reliabilities for individual items ranged from .85 on Fist-Edge-Palm to 1.0 on Delayed Recall. Major errors occurred in 48% of cases, with the most errors occurring on Fist-Edge-Palm, followed closely by Indicate Cubes. Over time, inter-rater reliabilities increased and errors decreased. Conclusion: Results indicate that intensive rater training on the SCOPA-COG can produce good to excellent inter-rater reliability. However, in spite of this training, almost half of the cases contained errors that affected the subjects' scores. Findings suggest that continuous training and surveillance on the SCOPA-COG is valuable, and emphasis can be placed on particular items to minimize error and thus increase study power.

#### **Learning Objectives:**

- To report inter-rater reliability for the SCOPA-COG following an intensive rater training program.
- To identify common errors on the SCOPA-COG that may benefit from training and surveillance.

#### **References:**

- Marinus J, et al. Assessment of cognition in Parkinson's disease. *Neurology*. 2003;61:1222-1228.
- Muller MJ & Szegedi A. Effects of Interrater Reliability of Psychopathologic Assessment on Power and Sample Size Calculations in Clinical Trials. *J Clin Psychopharm*. 2002; 22 (3): 318-325.

**Source of Funding:** Teva Pharmaceuticals

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#### **RISK-BASED MONITORING FOR ABERRANT RATING PATTERNS AND PATIENT SELECTION ANOMALIES IN GLOBAL SCHIZOPHRENIA TRIALS**

*Alan Kott, David Daniel*

*Bracket Global, LLC*

Background Risk-based outlier analysis of blinded data for aberrant rating patterns and patient selection anomalies can be paired with audio/video surveillance to cost effectively identify at-risk sites in global schizophrenia clinical trials. Methods Utilizing centralized, blinded data quality monitoring of 41,555 PANSS assessments in eleven international schizophrenia clinical trials, norms were created for a library of data patterns selected by sponsors as potentially at risk for measurement error or idiosyncratic patient selection. Based on these risk factors, a composite

score or “dashboard” was created ranking each site based on quality measures. Sites of concern were subsequently subjected to more intensive, remote, centralized review of recorded patient interviews by external experts. The quality of recorded interviews and ratings was remotely assessed by independent reviewers for 2,943 PANSS assessments. Results Based on independent review of audio and/or video recorded PANSS assessments, interview quality was rated as excellent, adequate with some deficiencies or inadequate in 75.44 % (n=2221), 23.2% (n=683) and 1.36% (n=40) of visits, respectively. Proper application of the PANSS instructions and anchor points was independently rated as excellent, adequate with some deficiencies, or inadequate in 75.98 % (n=2221), 22.8% (n=671) and 1.22% (n=36) of visits, respectively. The following illustrate examples of adaptive monitoring. Sites 397 and 762 were evaluated on three risk factors specified by the sponsor: 1) large between visit changes in the total PANSS score; 2) erratic PANSS changes; and 3) 100% identical PANSS scores from visit to visit. If anomalies were determined by blinded data monitoring, additional scrutiny was employed by external review of recorded patient visits. Site 397 was an outlier on factors 1 and 2 (> 3 SD above the mean) but refused to allow interviews to be recorded for external review to allow independent assessment of measurement error. The site was closed. Site 762 was not an outlier on large score or erratic score changes but more than 15% of visits were 100% identical. Recordings of patient interviews were scrutinized. The proportion of discordant PANSS ratings (>2 difference between site and independent rater) exceeded 60%. The site was subjected to remedial training and close scrutiny for the remainder of its trial participation. Discussion Risk based outlier analysis of blinded data for aberrant rating patterns and patient selection anomalies can be paired with audio/video surveillance to cost effectively identify at risk sites in global schizophrenia clinical trials. Allowing sites to “opt out” of audio/video surveillance complicates interpretation of data anomalies. In addition, audio/visual surveillance has the potential to identify endpoint scoring irregularities that may not emerge in outlier analysis. Additional data is being collected. The analyses reported above are preliminary.

### **Learning Objectives:**

- Understand how a combination of methodologies can produce more cost effective data monitoring results in clinical trials.
- Increase awareness of aberrant data patterns that may be associated with quality issues in clinical trials.

**Source of Funding:** Bracket Global, LLC

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### **FEASIBILITY, INTEGRITY AND EFFICIENCY OF THE SEQUENTIAL PARALLEL COMPARISON CLINICAL TRIAL DESIGN**

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*<sup>1</sup>Alkermes, Inc., <sup>2</sup>Massachusetts General Hospital Department of Psychiatry*

Background: Conditions with high placebo response present increasing challenges for clinical trial feasibility, integrity and efficiency. The two-stage Sequential Parallel Comparison Design (SPCD), developed by Fava et al., is an effective trial design to enable signal detection. Trials conducted with SPCD provide empirical evidence of its feasibility and efficiency. Simulation studies of several methods for statistical analysis support its integrity and efficiency. The present research expands on prior evidence, using extensive numeric simulation, informed by a

completed phase 2 SPCD trial in major depressive disorder (MDD). SPCD is further evaluated in the context of a comprehensive set of clinical trial design evaluation criteria. **Methods:** SPCD typically involves a two-stage clinical trial in which the second stage is enriched for placebo non-responders. SPCD's statistical performance was examined by simulation of change in total MADRS score, under wide assumption ranges for placebo response, treatment effect and variability, sample size and missing data. Analysis of simulated data employed stage-specific MMRM under assorted covariance matrices, and combined statistics across stages using a wide range of weights. Statistical performance parameters included type I error, accuracy, precision, power and inter-stage correlation. **Results:** Type I error was well-controlled, and estimation of the stage-specific treatment effect was accurate and precise across the simulation domain, using a stage-specific MMRM model with an unstructured covariance matrix. Correlation of treatment effect estimates across stages was negligible. SPCD was consistently more powerful and efficient than equivalent parallel-arm designs, with or without placebo lead-in. **Discussion:** SPCD's feasibility, integrity and efficiency were demonstrated in the context of comprehensive trial design criteria, including simulation of its statistical performance. Statistical inference was reliable, with well-controlled type I error, consistent accuracy and precision, across wide assumption ranges. SPCD showed robust efficiency, compared to parallel-arm designs. Negligible inter-stage correlation supports the validity of combined weighted inference. Combined inference may require nuanced clinical interpretation. SPCD is an acceptable trial design with the required feasibility, integrity and efficiency for use in confirmatory trials. SPCD has the potential to effectively mitigate risk of failure and increase efficiency in appropriate phase 2 to phase 4 clinical trials in MDD and other indications.

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- Chen YF, Yang Y, Hung HM, Wang SJ.: Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. *Contemp. Clin. Trials.* 2011; 32(4): 592-604.

#### **Learning Objectives:**

- To understand the current evidence of SPCD's feasibility, integrity and efficiency.
- To understand opportunities for further research and application of SPCD.

**Source of Funding:** Alkermes, Inc.

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#### **BLINDED DUAL RATINGS CONFIRM PRIMARY SITE-BASED RATINGS IN AN MDD TRIAL**

*Richard Leigh-Pemberton<sup>1</sup>, Asli Memisoglu<sup>1</sup>, Steven D. Targum<sup>2</sup>, J Cara Pendergrass<sup>2</sup>, Philip Rauh<sup>2</sup>, Randall D. Marshall<sup>1</sup>, Bernard L. Silverman<sup>1</sup>, Marc de Somer<sup>1</sup>, Elliot Ehrich<sup>1</sup>*

<sup>1</sup>*Alkermes, Inc.,* <sup>2</sup>*Clintara, LLC*

**Introduction:** The depression score ratings of site-based raters may be influenced by unintentional expectation bias, awareness of the study visit and previous ratings, or possible treatment-emergent events. One strategy to obviate the potential for site-based rater bias, affirm



ratings reliability, and to confirm study findings is to use a site-independent rater who is blinded to study visits and possible treatment effects. We obtained blinded “dual” ratings via audio-digital recordings of site-based interviews in a study in patients with major depressive disorder. Methods: Data were obtained from a quality assurance program developed by Clintara LLC for Alkermes’ study ALK5461-202: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate ALKS 5461 in Subjects with Major Depressive Disorder and Inadequate Response to Antidepressant Therapy (ClinicalTrials.gov: NCT01500200). The study used a sequential parallel comparison design method that included two study stages of four treatment weeks. The dual scoring analysis in this report examined 100% of the baseline- and end-of-first-stage- (week 4) ratings. Site-based raters administered both Hamilton (HAM-D17) and Montgomery-Åsberg (MADRS) rating scales for depression. Each interview was recorded with an audio-digital pen throughout the study. Site-independent raters who were blinded to the study visit or any possible treatment-emergent events generated distinct HAM-D17 and MADRS scores. Results: One hundred and thirty-five patients were randomized into stage 1 of the study. A comparison of all HAM-D17 and MADRS scores at baseline and end-of-stage 1 between the site-independent raters and site-based raters revealed a high correlation ( $r=0.93$  for the HAM-D17 and  $r=0.94$  for the MADRS) and minimal scoring discordance: HAM-D17 mean difference (SD) = 0.31 (2.8) points and MADRS mean difference (SD) = 0.15 (3.8). There were no statistically significant differences between the site-independent and site-based raters’ scores on the HAM-D17 and MADRS. The site-independent raters matched the site-based placebo response (28%) and essentially substantiated the site-based HAM-D17 and MADRS scores at baseline and after four weeks of double-blind treatment. Discussion: Dual ratings conducted by site-independent raters listening to audio-digital recordings of HAM-D17 and MADRS interviews corroborate the site-based findings in this positive study. The dual ratings methodology provided an effective quality assurance process and confirmed the findings generated by the primary site-based raters. References Targum et al., J Clin Psychopharmacol., 32: 2012 Targum et al., J. Psychiat. Res. 47: 2013

### **Learning Objectives:**

- To evaluate the use of site-independent dual ratings for quality assurance.

**Source of Funding:** Alkermes, Inc.

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### **COMPLEXITY IN PROTOCOL DESIGN: DOES IT LEAD TO BETTER CLINICAL TRIAL OUTCOMES?**

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Objective: In the current clinical research environment, biopharmaceutical companies face progressively limited financial resources along with increasing numbers of failed trials. Sponsors are seeking to reduce costs, improve study outcomes, and shorten the time it takes to bring new drugs to market. Protocol complexity has increased over the last fifteen years; however, it is unclear whether this trend in protocol design has helped to achieve these ends. This is a follow up poster examining more protocols and trial outcomes than the 2013 poster, which has increased statistical power. Method: Data were collected from 73, phase 2 through 4, double-

blind, placebo-controlled clinical trials conducted at CNS Healthcare from 2002 to 2011. The trials were assessed as successful or failed based on whether there was statistically significant separation of treatment from placebo on the primary efficacy measure. A one-sided t-test was used to assess whether the 2 groups differed on 3 measures of study complexity: 1) the number of eligibility criteria 2) the number of site visits in the trial, and 3) the average number of unique procedures per visit. Results: In our sample, there was no difference between successful and failed trials on the 3 measures of trial complexity. Conclusions: Clinical trial outcomes may not be benefiting from more complex trial design. Data-driven, more efficient trial design may strike a better balance between containing clinical trial cost and successful trial outcomes. Experienced research sites are in a unique position to work as partners with sponsors to optimize clinical trial design and improve trial outcomes.

### **Learning Objectives:**

- Outline protocol design components that have increased work burdens to cite protocol design.
- Discuss empirical support regarding improved clinical trial outcomes when using complex protocol designs.

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### **IMPACT OF BPRS INTERVIEW LENGTH ON RATINGS PRECISION DURING A SCHIZOPHRENIA TRIAL**

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Background Ratings precision is necessary to optimize signal detection in clinical trials, and is particularly important in studies that rely on subjective ratings. The ability of a second independent rater to replicate the scores given by the primary rater is one metric of ratings precision. We assessed ratings precision in a schizophrenia study using site-independent raters to blindly score audio-digital recordings of site-based interviews. Methods We examined ratings precision in a 12-week, double-blind, parallel-group study of PF-02545920 compared to placebo in patients with sub-optimally controlled symptoms of schizophrenia (ClinicalTrials.gov identifier NCT01939548). The study is currently being conducted at 26 trial centers in the United States. All patients consented to audio-digital pen recording of site-based interviews using the Brief Psychiatric Rating Scale (BPRS) as part of the screening assessment for subject eligibility. Recorded interviews were electronically transmitted to Clintara LLC (Boston MA) via a secure website and distributed to 5 site-independent reviewers. These reviewers were blinded to the study site and visit and scored the BPRS based upon the audio recording and corroborative digital information they received. We analyzed “dual” ratings concordance of the total BPRS score and the impact of interview length on the interviews received to date. Statistical analysis included intra-class correlation and Student’s t test. Results 105 BPRS interviews were submitted for “dual” scoring review at the time of this analysis. The mean total BPRS scores were  $50.1 \pm 7.6$  (SD) for the site-based raters and  $48.4 \pm 7.9$  for the site-independent reviewer/raters ( $t=1.55$ ;  $p=0.12$ ). The total BPRS scores of the paired “dual” site-independent raters were highly correlated with the site-based scores ( $r=0.815$ ), and the mean total BPRS scoring discordance (total score difference between site-based and site-independent raters) was  $1.3 \pm 4.6$  points for all subjects. Interview length significantly affected scoring discordance between site-based and site-independent ratings. The mean BPRS interview length was  $20:35 \pm 8:06$  minutes ranging from 7 to 60 minutes. 27 interviews (25.7%) were conducted in less than 15 minutes. These “shorter”

interviews yielded significantly greater scoring discordance ( $3.7 \pm 5.4$ ) than all other interviews ( $0.6 \pm 4.1$ ) in this analysis ( $t=2.39$ ;  $p=0.020$ ). Conclusion Overall, “dual” scoring of the site-based BPRS interviews revealed a high correlation and minimal scoring discordance between site-based and blinded, site-independent raters. However, interview length had a significant impact on “dual” ratings concordance such that “shorter” interviews ( $< 15$  minutes) were significantly more discordant than all other interviews in the sample ( $p = 0.02$ ). These data suggest that ratings precision may be compromised by short, incomplete interviews and may adversely affect the study outcome.

### **Learning Objectives:**

- To explore blinded, "dual" ratings in patients with acute psychosis.
- To examine challenges to achieve ratings precision of a primary measure in studies of acute psychosis.

**Source of Funding:** Pfizer Inc.

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### **ATTENUATION OF IMPULSIVITY IN BIPOLAR ALCOHOLICS WHO REDUCE HEAVY DRINKING: PROSPECTIVE EVIDENCE FROM A RANDOMIZED PLACEBO-CONTROLLED TRIAL**

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**Aims:** Alcohol dependence co-occurs more commonly in bipolar disorder than in any other Axis I diagnosis. Impulsivity is a core feature of both bipolar disorder and alcoholism. Prior research has shown that bipolar alcoholics have elevated trait impulsivity compared with individuals with either alcoholism alone or bipolar disorder alone. We have previously reported that abstinent bipolar alcoholics have lower trait impulsivity than their currently drinking counterparts. However, this cross-sectional finding cannot establish that impulsivity changes with abstinence, as abstinent individuals may have had lower levels of impulsivity prior to cessation of drinking. The current study prospectively evaluated changes in trait impulsivity in a sample of bipolar alcoholics with heavy current (past 30 days) drinking at baseline and 12 weeks after double-blind randomization to placebo or lamotrigine. **Methods:** Adults aged 18-65 who met DSM-IV criteria for bipolar I or II disorder and current alcohol dependence were eligible. Trait impulsivity was assessed using the Barratt Impulsiveness Scale (BIS-11). Mood symptoms were assessed with the Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI-II), and Young Mania Rating Scale (YMRS). Quantity and frequency of drinking and craving (Obsessive-Compulsive Drinking Scale (OCDS)) were recorded weekly over 12 weeks between impulsivity assessments. Baseline vs. endpoint changes in BIS-11 scores were analyzed by paired t-tests for each BIS-11 subscale. Pearson correlation coefficients were calculated for association between BIS-11 scores and mood scores, drinking outcomes (drinks/week, drinks/drinking day, percent days abstinent, percent heavy drinking days) and craving. **Results:** Of  $n=36$  subjects enrolled,  $n=20$  completed all assessments. Baseline BIS-11 scores were positively correlated with lifetime number of suicide attempts and with baseline BDI-II ( $R=.58$ ,  $p<.0001$ ), but not baseline MADRS ( $R=.07$ , N.S.) or YMRS ( $R=.16$ , N.S.) scores. BIS-11 total ( $p<.03$ ), attentional ( $p<.04$ ), and self-control ( $p<.02$ ) scores declined significantly from baseline to study endpoint. Change in BIS-11 scores correlated positively with change in percent heavy

drinking days and change in craving, but were not associated with change in drinks/week, drinks/drinking day, or percent days abstinent. Conclusions: "Trait impulsivity" as measured by the BIS-11 appears to have both trait and state properties in bipolar alcoholics. State properties of BIS-11 scores appear to be influenced by heavy alcohol use.

### **Learning Objectives:**

- Recognize the prevalence and impact of comorbid substance use disorders in individuals with bipolar disorder.
- Recognize that trait impulsivity is higher in individuals with bipolar disorder and co-occurring alcoholism than in individuals with either disorder alone but appears to be modifiable by abstinence from alcohol.

**Source of Funding:** NIAAA K23 017666

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### **EFFICACY OF QUETIAPINE-XR MONOTHERAPY OR ADJUNCTIVE THERAPY TO ANTIDEPRESSANT IN ACUTE MAJOR DEPRESSIVE DISORDER WITH GENERALIZED ANXIETY DISORDER: A RANDOMIZE, PLACEBO-CONTROLLED PILOT STUDY**

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Background: Comorbid anxiety disorders are highly prevalent in major depressive disorder (MDD). Quetiapine-XR has been shown to be significantly superior to placebo in reducing depressive symptom in “pure” MDD and anxiety symptoms in “pure” generalized anxiety disorder (GAD), but its efficacy in comorbid population remains unknown. The aim of this study was to pilot data on the efficacy of quetiapine-XR monotherapy or adjunctive therapy to antidepressant(s) in the acute treatment of MDD comorbid with GAD. Methods: The Mini International Neuropsychiatric Interview was used to ascertain the diagnosis of MDD, GAD, and other Axis I disorders. Eligible patients were randomly assigned to quetiapine-XR or placebo for up to 8 weeks. The Hamilton Depression Rating Scale-17 items (HAM-D-17) was used as the primary outcome to evaluate the differences between the two groups using the change from baseline to the end of study (EOS). Secondary outcome measures included the changes from baseline to EOS in Hamilton Anxiety rating scale (HAMA), Clinical Global Impression-Severity (CGI-S), Quick Inventory for Depression Symptomatology-16 items Self-Report (QIDS-16-SR), Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q), Sheehan Disability Scale (SD), response rate, and remission rate. Last observation carried forward and Mixed-effects modeling for repeated measures were used to analyze the primary and secondary outcome measures. Results: Of the 34 patients screened, 23 patients were randomized to receive quetiapine-XR (n=11) or placebo (n=12). Five patients in quetiapine-XR and 4 patients in placebo completed the study. Four in quetiapine-XR group and 1 in placebo group discontinued the study due to adverse events. The mean dose of quetiapine-XR was 154±91 mg/d. The change from baseline to EOS in the total scores of HAM-D-17, HAMA, QIDS-16, and CGI-S were significant in the quetiapine group, but, only the change in HAMA was significant in the placebo group. In the between group comparisons, the change from baseline to EOS in CGI-S was significantly larger in the quetiapine-XR group compared to that in the placebo group, 1.1 versus 0.2 points (p=0.036). The differences in the changes in HAM-D-17, HAMA, QIDS-16 were numerical larger, but not statistical significant, in the quetiapine-XR group compared to the

placebo group, with 8.4 versus 4.9 points for HAM-D17, 11.3 versus 8.3 points for HAMA, and 5.7 versus 2.1 points for QIDS-16, respectively. There were also no significant differences between the two groups in response rates based on  $\geq 50\%$  improvement in HAM-D-17 or HAMA total scores and remission rates based on HAM-D-17 total score of  $\leq 10$ . The changes in other secondary outcome measures were also not significantly different between the two groups. The most common side effects from quetiapine-IR were dry mouth and fatigue; and the most common side effects from placebo were insomnia and dizziness. Conclusion: In this pilot study, quetiapine-XR was numerically superior to placebo in reducing depressive and anxiety symptoms in patients with MDD and comorbid GAD. Large sample studies are warranted to support or refute these findings.

### **Learning Objectives:**

- Understand the efficacy of quetiapine-XR in major depressive disorder and comorbid generalized anxiety disorder.
- Understand the challenge of conducting clinical trials in patients with comorbid psychiatric conditions.

**Source of Funding:** AstraZeneca

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### **DOES ALGORITHM-BASED DEPRESSION CARE MITIGATE COGNITIVE DECLINE IN OLDER ADULT OUTPATIENTS?**

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Introduction: Older adults with MDD often present with cognitive complaints, and many exhibit cognitive impairment (Butters et al 2004). Evidence also suggests that MDD can contribute to persistent cognitive dysfunction, and is a risk factor for dementia (Diniz et al 2013). To investigate whether evidence-based MDD treatment modifies cognitive decline in an older outpatient population, we examined the impact of algorithm-based depression care on 1- and 2-year cognitive outcomes. We predicted that participants receiving algorithm-based (ALG) care would experience better cognitive outcomes (less decline on the MMSE) than participants receiving treatment-as-usual (TAU) care. Methods: We used data from PROSPECT, a multisite trial designed to assess a multi-component intervention for reducing late-life suicide (Bruce et al 2004). Participants were  $\geq$  age 60 and received treatment at an ALG or TAU primary care practice. Depressed participants at ALG practices received treatment from a depression care manager (following an algorithm that included antidepressant medication and/or IPT). Neuropsychological status was assessed yearly (Bogner et al 2007). We performed hypothesis-driven analyses to examine the relationship between treatment received and change in MMSE. MMSE totals were converted to Z-scores using means/SDs for age- and education-equated reference groups (Crum et al 1993). Mixed-models were run with depression status, time, and intervention added in stepwise fashion. Finally, demographic and clinical measures known to affect cognition (e.g., medical burden, depression severity) were included as covariates. Results: Of 1226 participants, 22% had impaired cognition ( $Z$ -MMSE  $< -1.0$ ) at baseline, compared to 40% at year 1 and 48% at year 2. Mixed models with/without covariates showed a significant time by diagnosis interaction (without:  $p < .01$ ,  $t = -3.13$ ,  $df = 1568$ ; with:  $p < .01$ ,  $t = -2.96$ ,  $df = 1456$ ), indicating that depressed participants had greater  $Z$ -MMSE decline than non-depressed controls. However, the interaction between intervention and decline was not statistically significant

(without:  $p=.12$ ,  $t=1.55$ ,  $df=1568$ ; with:  $p=.13$ ,  $t=1.52$ ,  $df=1456$ ), indicating that Z-MMSE decline for the ALG and TAU groups did not differ. When cognition was considered as a binary outcome (impaired vs. not), the time by diagnosis interaction remained significant ( $p<.01$ ,  $t=-2.73$ ,  $df=1209$ ) and the intervention component demonstrated a trend towards statistical significance ( $p=.098$ ,  $t=1.66$ ,  $df=1209$ ). Conclusions: Z-MMSE scores for all groups declined significantly over time, with greater decline among depressed participants. While depressed participants receiving ALG had slightly higher mean Z-MMSEs at years 1 and 2 (compared to TAU), the difference did not reach statistical significance. A notable shortcoming was the blunt nature of the MMSE, especially when used in non-demented individuals. In addition, the MMSE does not measure changes in executive functioning and information processing speed, two of the core features of depression-related cognitive impairment. For example, we have previously shown that treatment of MDD leads to gains in executive functioning among older patients with baseline cognitive impairment (Butters et al 2000). We plan to examine more sensitive measures of cognition in PROSPECT participants, with the goal of testing whether specific cognitive domains improve in older adults who receive algorithm-based care.

#### **Learning Objectives:**

- Over two years of follow-up, does cognitive function decline faster among outpatients with late-life depression, compared to non-depressed controls?
- In an outpatient population with late-life depression, does algorithm-based depression care improve cognitive outcomes, compared to treatment-as-usual?

**Source of Funding:** Supported by NIH R01s MH065539, MH072947 and MH080240, P30 MH090333, P50 AG005133, P60 MD000207, UL1s RR024153 and TR000005, the University of Pittsburgh Medical Center (UPMC) Endowment in Geriatric Psychiatry, and the John A. Hartford Foundation. In the past year, Dr. Koenig has received financial support from the APIRE/Janssen Resident Psychiatric Research Scholars program. The sponsors had no role in the design and conduct of the study; in data collection or management, analysis, and interpretation of the data; or in preparation, review, and approval of this abstract.

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#### **PRO-COGNITIVE EFFECTS OF KETAMINE AND UNDERLYING NEUROCIRCUITRY IN SUBJECTS WITH MDD AS ASSESSED BY FMRI AND NEUROPSYCHOLOGICAL TESTING**

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Context: Major depressive disorder (MDD) is associated with impairments in multiple cognitive domains including attention, learning, and memory. However, these cognitive dysfunctions are not targeted by current antidepressants. Moreover, the underlying neural mechanisms are not fully understood. Glutamate signaling and synaptic plasticity, both of which are impaired in MDD, are a mainstay of normal cognitive functioning. Ketamine, an NMDA antagonist with rapid-acting antidepressant properties, has been shown to normalize glutamate signaling and synaptic plasticity in animal models of depression. Interestingly, the enhanced neuroplasticity is evident 24-hours following a single sub-anesthetic dose of ketamine, which coincides with the peak of the drug's antidepressant effects in humans and with enhanced cognitive functions as demonstrated by mounting preclinical evidence. Our preliminary MDD data suggest

improvements in cognitive performance and in functional connectivity in the left dorsolateral prefrontal cortex (DLPFC) 24-hours post single infusion of ketamine. Aim: To determine the pro-cognitive effects and underlying neurocircuitry of a single intravenous ketamine administration in subjects diagnosed with MDD. Methods: Eighteen medication free subjects aged 18-65 with a diagnosis of MDD will be recruited. Subjects will complete an evaluation including fMRI, mood symptom inventories, and a short, yet comprehensive neuropsychological battery including CogState (a computerized assessment designed to detect changes in cognitive performance over time). Evaluations will be conducted at baseline and 24-hours following a ketamine hydrochloride infusion of 0.5 mg per kg infused over 40 minutes. Expected Results: We hypothesize that the administration of a single sub-anesthetic dose of intravenous ketamine in MDD subjects will produce cognitive enhancement and increased neural connectivity 24 hours post-administration. We predict a positive relationship between cognitive enhancement and increased left DLPFC connectivity, as measured by weighted Global Brain Connectivity (wGBC). Current preliminary data and any data obtained by the June ASCP/NCDEU meeting will be reported. Conclusion: The rapid effects of ketamine on synaptic plasticity provide a unique paradigm to examine the underlying neurocircuitry of cognitive performance as related to neuroplasticity. This paradigm will also allow us to look beyond the specific antidepressant effects of ketamine to evaluate the potential for rapid pro-cognitive effects, which has significant positive implications for patients with MDD and several other psychiatric disorders with impaired cognitive functions.

#### **Learning Objectives:**

- Further understanding of ketamine's effect on cognitive performance in human subjects, 24-hours following a single sub-anesthetic administration, through data obtained by fMRI and neuropsychological assessment.
- Further understanding into the underlying neurocircuitry of cognitive performance and increased connectivity in human subjects.

**Source of Funding:** This study is supported by a K23 Award. (K23MH101498; NIMH) Chadi Abdallah (PI) 08/05/13 – 07/31/18

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#### **CONFIRMING MDDSCORE AS AN AID IN THE DIAGNOSIS OF MAJOR DEPRESSIVE DISORDER**

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Background: Previously a biomarker panel was developed for use as an aid to MDD diagnosis; it consisted of nine biomarkers associated with the neurotrophic, metabolic, inflammatory and hypothalamic-pituitary-adrenal (HPA) axis pathways [Papakostas et al. Mol. Psych. 18:332, 2013]. This panel and associated algorithm demonstrated good clinical sensitivity and specificity (92% and 81% respectively) in differentiating MDD patients from normal healthy individuals. In order to further validate the panel, we performed a prospective study using a larger set of new sequentially acquired MDD patients and a similarly collected population of healthy, non-MDD

subjects. The addition of gender and BMI effects to the algorithm was also evaluated. Methods: Blood samples were obtained from MDD patients (n=68), clinically evaluated at multiple sites using standard psychiatric assessment tools and structured clinical interviews. Blood samples (n=86) from normal subjects were obtained as controls. MDD and normal samples were randomized into independent training (n=102) and validation sets (n=52). Serum biomarkers were quantified by immunoassay. Results: Training set biomarker data were used to develop a logistic regression model that included gender and BMI in a manner that allowed for their interaction with the biochemical analytes. The sensitivity and specificity of the panel for the training set was 93% (CI=0.80-0.98) and 95% (CI=0.85-0.99), respectively. This method was then applied to the independent validation set and the panel had a sensitivity and specificity of 96% (CI=0.77-0.99) and 86% (CI=0.66-0.95), respectively. The overall accuracy for the training and validation sets was 94% and 91%, respectively. Conclusions: Examination of a randomized independent set of samples confirms the ability of the previously established biomarker panel to identify persons with MDD; the accuracy was over 90%. Use of the MDDscore biomarker panel and algorithm provides a mechanism to objectively stratify patients for clinical trials.

### **Learning Objectives:**

- Demonstrate the ability of a 9 member biomarker panel and a logistic regression model which includes the interaction of gender and BMI with serum analytes to segregate MDD patients from normal subjects.
- Indicate the utility of the test as an aid to clinical diagnosis and in the stratification of patients for clinical trials of therapeutic regimens.

**Source of Funding:** This study was funded in entirety by Ridge Diagnostics Inc.

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### **THE EFFECT OF VORTIOXETINE ON SEXUAL DYSFUNCTION DURING THE TREATMENT OF ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD) OR GENERALIZED ANXIETY DISORDER (GAD)**

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Background: Many MDD and GAD patients suffer from sexual dysfunction, and treatments may impair sexual function. Vortioxetine's multimodal mechanism of action includes direct modulation of receptor activity and serotonin transporter inhibition.<sup>1</sup> Vortioxetine receptor profile and preclinical data support limited sexual dysfunction. Objective To evaluate the incidence of treatment-emergent sexual dysfunction (TESD) for vortioxetine 5-20mg/day, duloxetine 60mg (DUL) and placebo (PBO) in subjects with MDD or GAD and no baseline sexual dysfunction. The primary objective was to confirm similarity of vortioxetine to PBO. Secondary analyses include a pre-specified comparison of vortioxetine and DUL. Methods The Arizona Sexual Experience Scale (ASEX) was used to assess sexual function in 6 short-term MDD studies [NCT00635219, NCT01140906, NCT01153009, NCT01163266, NCT01179516, and NCT00672620] and 1 GAD study [NCT00730691] using the dichotomous method of McGahuey.<sup>2</sup> Non-inferiority was evaluated using the common risk difference in TESD incidence rates between vortioxetine and PBO in subjects who developed sexual dysfunction, with a clinically meaningful margin of 10%. Results Nearly 30% of randomized subjects had no baseline sexual dysfunction (PBO, 309/1088 [28.4%]; vortioxetine 5-20mg, 580/1985 [29.2%];



DUL, 226/756 [29.9%]). The pooled incidences of developing TESD at any timepoint in the study were PBO 32.0% (range 24.7 to 46.7%), vortioxetine 5-20mg 37.1% (21.9 to 60.0%), and DUL 48.2% (43.9 to 60.0%). TESD rates for vortioxetine 5mg, 10mg and PBO were generally similar, except for a higher rate for 10mg in NCT01163266. Separation of DUL from PBO confirmed assay sensitivity. In 5 studies with DUL, TESD rates for vortioxetine 5-20mg were lower than for DUL, except in NCT01140906, where a higher rate was observed for VORT 15 and 20mg. Common risk difference estimates for developing TESD increased with vortioxetine dose (5mg, -4.6%; 20mg, 9.9%) vs PBO. Vortioxetine 5mg was noninferior to PBO, with TESD incidence rates for vortioxetine 10, 15, and 20mg not statistically significantly higher vs PBO. Overall, the common risk difference to PBO for developing TESD was not statistically significantly different for vortioxetine 5-20 mg (4.2%, 95%CI -2.4;10.7). DUL had a statistically significantly higher common risk difference of TESD vs. PBO (15.0%, 95% CI 5.8;24.1), with a statistically significantly lower risk noted for vortioxetine 5mg (-22.0%, 95% CI -33.5;-10.6) and 10mg (-19.6%, 95% CI -33.5;-5.7) relative to DUL. Subgroup (age, sex) results were generally consistent with overall results. Conclusions: The risk of developing TESD for MDD or GAD patients without baseline sexual dysfunction was not statistically significantly different between vortioxetine doses (5-20mg/day) and PBO with non-inferiority demonstrated at 5mg. The risk of developing TESD was higher with DUL compared to PBO and vortioxetine 5 and 10mg.

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#### Learning Objectives:

- Evaluate and understand the sexual function profile of vortioxetine in MDD and GAD patients.
- Compare the sexual function profile of vortioxetine to PBO and DUL.

**Source of Funding:** This study was funded by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S.

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#### **THE EFFECTS OF BUPRENORPHINE AND SAMIDORPHAN, ALONE AND IN COMBINATION, ON MONOAMINE RELEASE WITHIN THE NUCLEUS ACCUMBENS SHELL AND MEDIAL PREFRONTAL CORTEX OF MALE WISTAR RATS**

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ALKS 5461 represents a novel treatment for depression that combines buprenorphine (BUP), a partial mu agonist, with samidorphan, a potent mu antagonist. ALKS 5461 was recently studied as adjunctive therapy in subjects having an inadequate response to antidepressants in a phase 2, sequential parallel comparison design trial, and was found to be superior to placebo on a range of primary and secondary measures of depressive symptoms. These clinical findings are consistent with a substantial body of non-clinical and pharmacologic research indicating that endogenous

opioid systems regulate mood and are dysregulated in depressive illness [Berrocoso, 2009; Kennedy, 2006]. In addition, opioid receptors and their endogenous ligands are expressed in areas of the brain that have been associated with depression including the mesolimbic system. These microdialysis studies were designed to investigate the effects of BUP and samidorphan, alone and in combination, on extracellular concentrations of monoamines in the nucleus accumbens shell (NAc-sh) and the medial prefrontal cortex (mPFC). Within the NAc-sh, BUP (0.01-1 mg/kg) produced a dose-dependent elevation in extracellular DA. Administration of samidorphan had no effect on extracellular concentrations of DA or the monoamine metabolites DOPAC, HVA or 5-HIAA at any dose. When samidorphan (0.3 and 1.0 mg/kg) was co-administered with BUP, increases in extracellular DA, DOPAC, HVA and 5-HIAA were attenuated, but not entirely blocked. However, 3.0 mg/kg samidorphan completely blocked BUP-induced increases in extracellular DA, DOPAC, HVA and 5-HIAA. In the mPFC, treatment with samidorphan had no effect on extracellular DA, NE or 5-HT. BUP (0.01-1 mg/kg) resulted in maximal increases in DA and 5-HT of approximately 215% and 240%, respectively. Samidorphan dose-dependently attenuated BUP-induced increases in extracellular DA and 5-HT in the mPFC. Dysregulation of the endogenous opioid system has been postulated to play an important role in mood disorders. Exogenous opioids, including BUP, have beneficial effects in treating depression. In these studies, BUP caused increased extracellular concentrations of monoamines and their metabolites in the NAc-sh and mPFC. In contrast samidorphan, an opioid modulator with potent mu receptor antagonist activity, had no effect on monoamine release within these regions of the mesolimbic system. Regional differences in the magnitude of the monoamine response to BUP were noted, as well as regional differences in the effect of BUP when given in combination with samidorphan at clinically relevant doses. These studies indicate that differential modulation of monoamine release within the mesolimbic system may contribute to the efficacy of ALKS 5461 in the treatment of depression.

#### **Learning Objectives:**

- Participants will learn about a new drug combination, buprenorphine and samidorphan, as a novel and potential treatment for major depressive disorder with attributes that may contribute to an enhanced safety and efficacy profile.
- Participants will learn about the utility of modulating full or partial mu agonist activity to yield potential drug candidates with decreased risk of abuse, yet maintained efficacy.

**Source of Funding:** All studies were funded by Alkermes, Inc.

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#### **THE NEUROCIRCUITRY OF INCREASED INFLAMMATION IN DEPRESSION: PRELIMINARY FINDINGS**

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There has been increasing interest in the role of inflammation and inflammatory cytokines in depression, and recent neuroimaging data from our group and others suggest that inflammatory cytokines target the basal ganglia to contribute to depressive symptoms. These findings have included cytokine and inflammation-induced decreases in neural activation of the ventral striatum to hedonic reward and decreased amphetamine-induced striatal dopamine release, which

correlated with symptoms of depressed mood, anhedonia, and/or psychomotor slowing. In addition to effects on the basal ganglia, the administration of cytokines or cytokine inducers (e.g. vaccination) has been shown to increase activity of the anterior cingulate cortex (ACC), which may be particularly relevant to symptoms of anxiety, depressed mood, and anhedonia. The present pilot study examined whether the effects of increased inflammation (defined as  $\text{CRP} \geq 3$ ) on the basal ganglia affects functional connectivity between the striatum and other brain regions (e.g. ACC) to mediate symptoms of anxiety, depressed mood, anhedonia and psychomotor slowing. Wakeful resting-state fMRI data were acquired from 17 currently depressed patients (11 with low inflammation,  $\text{CRP} = 0.64 \pm 0.53$ ; 6 with high inflammation  $\text{CRP} = 6.4 \pm 2.9$ ). Four striatal seeding regions in each hemisphere were predefined, and seed-to-whole brain correlations were computed and compared between groups. Compared to depressed patients with low inflammation, depressed patients with high inflammation exhibited attenuated functional connectivity between three of the four striatal seeds, ventral striatum (VS), ventral rostral putamen, and dorsal caudate putamen (DCP), and thirteen other cortical or subcortical brain regions. Of these thirteen significant relationships, decreased connectivity between the left DCP and left anterior prefrontal cortex, left VS and left middle temporal gyrus, and right VS and left amygdala correlated with psychomotor slowing, as measured by the Trail Making A test. Furthermore, decreased connectivity between both the left VS and left rostral ACC (BA 32) and the right VS and right amygdala, correlated with increased depression scores as measured by the Inventory of Depressive Symptomatology-Self Report (IDS-SR), and specifically with symptoms of anxiety and anhedonia. These findings suggest that inflammation-related attenuation of connectivity between VS and both the rostral ACC and amygdala may mediate symptoms of anxiety and anhedonia, whereas compromise of frontostriatal circuits related to affective and cognitive processing may be related to decreased psychomotor performance. This preliminary study is the first to describe the neurocircuitry of behavioral symptoms in patients with increased inflammation and depression.

### **Learning Objectives:**

- Inflammation and inflammatory cytokines affect the basal ganglia and disrupt striatal connectivity with other brain regions.
- Inflammation-related compromise of frontostriatal circuits may mediate symptoms of anxiety, anhedonia, and psychomotor slowing in depressed patients with increased inflammation.

**Source of Funding:** This work was supported by funds from the National Institute of Mental Health (R01MH087604 and K23MH091254), and by PHS Grants UL1TR000454 and KL2TR000455 from the National Center for Advancing Translational Sciences of the National Institutes of Health.

### **ANHEDONIA AND IRRITABILITY AS CORRELATES OF ADVERSE CLINICAL FEATURES IN ADOLESCENT MAJOR DEPRESSION**

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Background: Adolescent MDD is a major public health concern, and yet, up to 40% of diagnosed teens fail to respond to evidence-based anti-depressant treatments. The major challenge has been that the categorical diagnosis of MDD relies on a cluster of symptoms most likely derived from different etiologies and does not capture the continuum of symptoms. In response, there has been increasing recognition for the importance of studying symptoms quantitatively. Thus, here we examine anhedonia and irritability, both core symptoms of MDD that manifest a wide severity range, in relation to other dimensional measures of illness severity (e.g., suicidality and episode duration). Methods Ninety adolescents with MDD ages 12-20 were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL). Depression severity was assessed by the clinician-rated Children's Depression Rating Scale—Revised (CDRS-R) and the self-rated Beck Depression Inventory second edition (BDI-II), and suicidality was quantified by the Beck Scale for Suicidal Ideation (BSSI). Anhedonia and irritability severity were each assessed by a sum of symptom-related items from the CDRS-R and BDI-II. Results Distribution: Severity range of both irritability [mean (SD), 5.13 (1.81), range: 1-9] and anhedonia [6.46 (2.70), range: 1-13] was wide. A correlation analysis indicated that anhedonia and irritability were not significantly correlated. Irritability: Irritability was not significantly correlated with illness severity (computed by CDRS-R without the irritability-related item). Additionally, irritability was not significantly associated with any adverse clinical feature (number of MDD episodes, the duration of the current episode, suicidality scores, or the numbers of suicide attempts). Anhedonia: Unlike irritability, anhedonia was significantly correlated with illness severity (computed by CDRS-R without the anhedonia question;  $r = 0.495$ ,  $p < 0.001$ ); therefore, illness severity was entered as a covariate in all subsequent analyses with anhedonia. Anhedonia severity was associated with the number of MDD episodes ( $F = 7.09$ ,  $p = 0.009$ ), the duration of the current MDD episode ( $F = 6.02$ ,  $p = 0.016$ ) and suicidality scores ( $F = 4.68$ ,  $p = 0.03$ ); however, it was not associated with the number of reported suicide attempts. Conclusions While both anhedonia and irritability serve as core symptoms for adolescent depression, and both manifest full range of severity, only anhedonia seems to be related to suicidality scores and illness duration. These findings further support the need to dimensionally examine specific phenotypes of adolescent MDD in order to develop personalized and more effective interventions.

### Learning Objectives:

- To consider a dimensional investigative approach to studying adolescent depression.
- To assess anhedonia and irritability as correlates of adverse clinical features, including suicidality and illness duration.

**Source of Funding:** This study was supported by NIH grants AT004576, MH095807.

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### A DUAL-PROBE MICRODIALYSIS INVESTIGATION OF THE INTERACTION BETWEEN LISDEXAMFETAMINE DIMESYLATE (LDX) AND S-CITALOPRAM ON CNS MONOAMINES – EVIDENCE FOR SYNERGISTIC AUGMENTATION OF SEROTONIN AND DOPAMINE EFFLUX

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<sup>1</sup>Renasci, Ltd, <sup>2</sup>Shire

Background: Lisdexamfetamine dimesylate (LDX), a prodrug of d-amphetamine, is approved to treat ADHD. Intracerebral microdialysis has shown that LDX produces substantial and

prolonged increases of noradrenaline and dopamine efflux in the prefrontal cortex (PFC) and striatum (1). These neurochemical effects would be predicted to complement the therapeutic actions of the SSRIs if they were co administered. We have investigated the interaction between LDX and S citalopram by dual probe microdialysis to determine the neurochemical profiles of LDX and S-citalopram alone and together. Methods Male Sprague Dawley rats were stereotaxically implanted with two microdialysis probes into hippocampus [HIPP] (4 mm tip, AP: 4.8 mm; L: +/- 4.8 mm relative to bregma; V: 7.8 mm relative to the skull surface) and nucleus accumbens [ACC] (2 mm tip, AP: +2.2 mm; L: +/- 1.5 mm; V: 8.0 mm) or PFC (2 mm tip, AP: +3.2 mm; L: +/- 2.5 mm; V: 4.0 mm) and striatum [STR] (4 mm tip, AP: +0.2 mm; L: +/- 3.0 mm; V: 7.8 mm (2). The following day after collection of 3 basal samples rats (n = 7-8) were given vehicle (po)/vehicle (ip), LDX (1.5 mg/kg d amphetamine base po)/vehicle (ip); vehicle (po)/S-citalopram (5 mg/kg, ip) or LDX (1.5 mg/kg, po)/S citalopram (5 mg/kg, ip). Noradrenaline, dopamine and 5 HT were quantified by reverse-phase, ion-pair, HPLC-ECD. Results S Citalopram increased 5 HT efflux in HIPP (AUC [0 3.0hr] = 427%; p<0.01), ACC (392%; p<0.05) and striatum (288%; p<0.01), but not PFC. S Citalopram had no effect on extracellular noradrenaline or dopamine in any region. LDX increased noradrenaline and dopamine in HIPP (403%; p<0.05; 268%, p<0.001, respectively) and PFC (194%; p<0.05; 195%, p<0.001, respectively). LDX increased dopamine, but not noradrenaline, efflux in ACC (253%; p<0.001) and STR (229%; p<0.001). Combining LDX with S-citalopram increased extracellular noradrenaline and dopamine in PFC, all 3 monoamines in HIPP, and dopamine and 5 HT in ACC and STR. Thus, the complementary actions of these two compounds on monoaminergic neurotransmission were realized when they were administered in combination. There was clear synergistic augmentation of S citalopram induced 5 HT efflux in HIPP (1089%; p<0.001), ACC (521%; p<0.05) and STR (561%; p<0.001). S Citalopram profoundly augmented the effect of LDX on dopamine efflux in the STR (536%; p<0.001). Conclusions LDX increased noradrenergic and dopaminergic neurotransmission to complement SSRI-enhanced 5 HT efflux. Importantly there was a synergistic effect of LDX + S citalopram on 5 HT efflux in the HIPP and 5-HT and DA efflux in the STR. These data suggest that a more extensive engagement of monoaminergic neurotransmission was achieved by the combination of LDX and S-citalopram than S-citalopram alone.

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#### Learning Objectives:

- Define the neurochemical profiles of LDX and S citalopram, alone and in combination, in different brain regions.
- Determine if the combination of S citalopram and LDX may enhance monoaminegic transmission more extensively in the CNS than S citalopram alone.

**Source of Funding:** Shire Pharmaceuticals

# **DETERMINATION OF THE MONOAMINERGIC INTERACTIONS BETWEEN LISDEXAMFETAMINE DIMESYLATE (LDX) AND DULOXETINE REVEALS A SYNERGISTIC AUGMENTATION OF DOPAMINE EFFLUX IN THE NUCLEUS ACCUMBENS AND STRIATUM**

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Background LDX, a prodrug of d-amphetamine, is approved to treat ADHD. We previously used dual probe, intracerebral microdialysis in rats to explore the effects of combining LDX with the SSRI, S-citalopram, on monoaminergic changes in several regions of the rat brain (1). In this study, we have used the same technique to determine the neurochemical profiles of LDX and the serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant duloxetine, alone and in combination. Methods Male Sprague Dawley rats were stereotaxically implanted with two concentric microdialysis probes (CMA, Sweden) into hippocampus [HIPP] (4 mm tip, AP: 4.8 mm; L: +/- 4.8 mm relative to bregma; V: 7.8 mm relative to the skull surface) and nucleus accumbens [ACC] (2 mm tip, AP: +2.2 mm; L: +/- 1.5 mm; V: 8.0 mm) or prefrontal cortex [PFC] (2 mm tip, AP: +3.2 mm; L: +/- 2.5 mm; V: 4.0 mm) and striatum [STR] (4 mm tip, AP: +0.2 mm; L: +/- 3.0 mm; V: 7.8 mm (2). The following day after collection of 3 basal samples, rats (n = 7-8) were given vehicle (po)/vehicle (ip), LDX (1.5 mg/kg d amphetamine base po)/vehicle (ip); vehicle (po)/duloxetine (5 mg/kg, ip) or LDX (1.5 mg/kg, po)/duloxetine (5 mg/kg, ip). Noradrenaline, dopamine and 5 HT were quantified by reverse-phase, ion-pair, HPLC-ECD. Results Duloxetine increased noradrenaline and 5 HT efflux in PFC (AUC[0-3.0hr] = 293%, p<0.01; 168%, p<0.05, respectively) and HIPP (274%, p<0.05; 650%, p<0.001, respectively) and 5 HT in STR (479%; p<0.01). Duloxetine also increased extracellular dopamine in PFC (218%, p<0.05) and HIPP (220%, p<0.001). LDX increased extracellular noradrenaline and dopamine in PFC (449%; p<0.001; 264%, p<0.01, respectively). LDX increased dopamine, but not noradrenaline, efflux in HIPP (263%; p<0.001), ACC (282%; p<0.001) and STR (197%; p<0.001). 5-HT was unaffected by LDX in all regions examined. Combining LDX with duloxetine increased extracellular noradrenaline and dopamine in PFC, all 3 monoamines in HIPP, dopamine and 5 HT in STR and dopamine in ACC. Thus when administered in combination, the complementary actions of LDX and duloxetine on monoaminergic neurotransmission were realized in all regions. The possible exception was the PFC where the findings were equivocal. There was a synergistic augmentation of LDX induced dopamine efflux in ACC (377%; p<0.05) and STR (315%; p<0.001). Conclusions LDX contributes increased dopaminergic neurotransmission in PFC, HIPP, ACC and STR to complement the increases of noradrenaline and 5 HT in PFC and HIPP, and 5 HT in STR evoked by duloxetine. Combining duloxetine with LDX synergistically augmented the effect of LDX on dopamine efflux in ACC and STR. These findings suggest that the combination of duloxetine and LDX may enhance monoaminergic transmission more extensively in the CNS than duloxetine alone.

## **References:**

- Heal DJ, Rowley HL, Kulkarni RS, Hutson PH: 2014; this meeting.
- Paxinos G, Watson C: The Rat Brain in Stereotaxic Coordinates, 2nd Edn. 1986; Academic Press.

## **Learning Objectives:**

- Define the neurochemical profiles of LDX and duloxetine, alone and in combination, in different brain regions.
- Determine if the combination of duloxetine and LDX may enhance monoaminegic transmission more extensively in the CNS than duloxetine alone.

**Source of Funding:** Shire Pharmaceuticals

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# **SAFETY AND TOLERABILITY OF VORTIOXETINE 15 AND 20 MG IN SUBJECTS WITH MAJOR DEPRESSIVE DISORDER (MDD): A PHASE 3, LONG-TERM, OPEN-LABEL EXTENSION STUDY**

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Background: Vortioxetine was approved in 2013 for the treatment of adults with MDD. Its mechanism of action is thought to be multimodal, combining the direct modulation of serotonin receptor activity with inhibition of the serotonin transporter.<sup>1,2</sup> Objectives: The primary endpoint was the long-term safety and tolerability of flexible doses of vortioxetine 15 and 20 mg in MDD subjects. The secondary endpoint was its clinical effectiveness using measures of depression, anxiety, and disability. Methods: This was a 52-week, flexible-dose, open-label extension (OLE) trial (NCT01152996) of subjects who had completed 1 of 3 previous short-term MDD studies of vortioxetine (NCT01153009, NCT01163266, or NCT01179516). All subjects were switched to vortioxetine 10 mg/day for the first week of treatment, with subsequently increases to 15 or 20 mg/day based on the investigator's clinical judgment. Safety and tolerability were assessed by treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms, laboratory values, physical examination, with suicidality measured with the Columbia Suicide Severity Rating Scale (C-SSRS). Efficacy measures included the Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAM-A), Clinical Global Impression-Severity of Illness Scale (CGI-S) and Sheehan Disability Scale (SDS). Results: Of 1075 subjects enrolled, 1073 received 1 or more doses of vortioxetine, and 538 (50.0%) completed the study. Of the 537 early withdrawals, 142 (13.2% of original population) withdrew consent, 115 (10.7%) withdrew due to TEAEs, 112 (10.4%) were lost to follow-up, and 68 (6.3%) cited lack of efficacy. TEAEs were reported by 854 subjects (79.6%), with 34 serious adverse events (SAEs) in 29 subjects (2.7%), 11 of whom (1.0%) withdrew. SAEs occurring in more than one patient included acute cholecystitis (n=2); breast cancer (n=3); and suicide attempt (n=3). No deaths occurred. Long-term treatment with vortioxetine was well tolerated; TEAEs reported by ≥5% of subjects included nausea (24.0%), headache (12.7%), diarrhea (7.5%), vomiting (6.3%), constipation (6.1%), weight increase (6.1%), and insomnia (5.2%). Laboratory values, vital signs, and physical examinations revealed no trends of clinical concern. Mean MADRS total score was 32.8 at double-blind baseline, 19.9 at the start of the OLE, and 11.9 at the final visit (observed cases [OC]). Mean HAM-A score was 18.8 at double-blind baseline, 11.5 at the start of the OLE, and 7.8 at the final visit (OC). Maintenance of improvement was also seen in mean CGI-S and SDS scores. Conclusions: Long-term vortioxetine 15 and 20 mg were safe and well tolerated. Subjects continued to improve on primary and secondary measures throughout the open-label treatment period.

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### **Learning Objectives:**

- To understand the long-term safety/tolerability of vortioxetine in adults with MDD.
- To evaluate the long-term clinical efficacy of vortioxetine in adults with MDD.

**Source of Funding:** This study was funded by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S.

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### **EFFICACY AND SAFETY OF VILAZODONE 20 MG AND 40 MG IN MAJOR DEPRESSIVE DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED TRIAL**

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**Introduction:** Vilazodone (VLZ) is a potent serotonin reuptake inhibitor and 5-HT<sub>1A</sub> receptor partial agonist approved for the treatment of major depressive disorder (MDD) in adults. The efficacy and safety of 40-mg VLZ was established in 2 randomized, placebo-controlled trials. The objective of this study was to assess the efficacy and safety of once-daily VLZ 20mg and 40mg in adults with MDD. **Methods:** This study (NCT01473381) was a multicenter, randomized, double-blind, placebo- and active-controlled, fixed-dose study in MDD patients comparing VLZ 20mg/d and VLZ 40mg/d with placebo (PBO); citalopram 40mg/d (CIT) was included for assay sensitivity. Primary efficacy outcome was change from baseline to Week 10 in Montgomery-Åsberg Depression Rating Scale (MADRS) score; secondary outcomes were change in Clinical Global Impressions-Severity (CGI-S) and MADRS sustained response rate (total score ≤12 for at least the last 2 consecutive visits). For the VLZ groups, P values were adjusted to control for multiple comparisons. Safety assessments included adverse events (AEs), laboratory and vital sign measures, ECG, Columbia-Suicide Severity Rating Scale (C-SSRS), and Changes in Sexual Functioning Questionnaire (CSFQ). **Results:** The safety population comprised 281 placebo, 288 VLZ 20mg, 287 VLZ 40mg, and 282 citalopram patients; discontinuation rates were 25%, 31%, 34%, and 29%, respectively. MADRS score improvement was significantly greater for VLZ 20mg (LSMD, -2.57; adjusted P=.0073), VLZ 40mg (LSMD, -2.82; adjusted P=.0034), and CIT (LSMD, -2.74; P=.0020) compared with placebo. Reduction in CGI S scores were significantly greater than PBO for VLZ 20mg (LSMD, -0.35; adjusted P=.0073), VLZ 40mg (LSMD, -0.33; adjusted P=.0097), and CIT (LSMD, -0.35; P=.0025). More patients met criteria for MADRS sustained response in the VLZ 20mg (29.9%), VLZ 40mg (33.5%), and CIT (31.1%) groups versus placebo (26.3%); differences were not statistically significant. Rates of treatment-emergent AEs (TEAEs) were similar for VLZ 20mg (72.2%), VLZ 40mg (77.4%), and CIT (77.0%) and placebo (63.3%). TEAEs occurring in ≥5% of vilazodone patients and twice placebo were diarrhea, nausea, vomiting, and insomnia. Majority of TEAEs were mild or moderate in severity. Serious AEs (SAEs) were reported in 2 placebo, and 4 VLZ 20mg, 4 VLZ 40mg, and 6 CIT patients. Both VLZ groups had greater improvement on the CSFQ relative to citalopram; differences were not statistically significant. **Conclusion:** Significantly greater



improvement was observed in MADRS and CGI-S scores for VLZ 20mg and 40mg and citalopram 40 mg versus placebo. Rates of MADRS sustained response were higher for both VLZ groups and citalopram compared with placebo, but the differences were not statistically significant. VLZ was generally well tolerated. These results support the efficacy, safety, and tolerability of VLZ 20mg and 40mg for the treatment of MDD in adults.

#### **Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the efficacy of vilazodone 20mg and 40mg and citalopram in adult patients with MDD.
- At the conclusion of this session, the participant should be able to evaluated the safety and tolerability of vilazodone and citalopram.

**Source of Funding:** Supported by funding from Forest Laboratories, Inc.

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#### **OPTIMIZING THE RESPONSE TO TMS IN MAJOR DEPRESSION THROUGH INTENSIVE CONCOMITANT MEDICATION MANAGEMENT**

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**Purpose** The purpose was to document the outcome in patients with treatment resistant major depression (TRD) when transcranial magnetic stimulation (TMS) was combined with intensive medication management. Our hypothesis was that optimum outcome could be obtained by combining TMS with intensive medication management. **Content** While many agents have been proven to be effective as antidepressants, some patients with depression don't respond or relapse while taking them. A recent review found pooled response/remission rates 29.3 and 18.5% respectively<sup>1</sup> for TMS in major depression. Most of the studies conducted when medication was allowed seemed to utilize only one antidepressant. **Methods** This was an open-label naturalistic outpatient study of patients with TRD. TMS was initiated upon consent utilizing the Neurostar® device and applied according to the guidelines recommended by the manufacturer. Rating scales were done initially and weekly using the Montgomery Asberg Depression Rating Scale (MADRS) while the patients completed the Patient Health Questionnaire (PHQ-9); rapid changes in medication were made when warranted. TRD was defined by history of at least one failed adequate trial of antidepressant medication. A total of 55 patients participated. The age range was 15-92 years (M=46). The current episode had a mean duration of 79 months and the mean initial MADRS was 32. The patients had failed an average of 3 adequate antidepressant trials and a total of 1.7 inadequate trials. Current episode failed augmentation trials averaged 5.7. **Results** There were a total of 40 patients (73%) that responded to treatment (50% reduction in MADRS score) and 30 patients (55%) that achieved remission ( $\leq 8$  on the MADRS). Of those who achieved response or remission, 64% had failed more than one adequate antidepressant trials in the current depressive episode. Patients that responded had significantly lower MADRS scores two weeks after the last medication change (M=7.2) compared to the weeks prior to (M=11.6) and immediately following (M=10.6). **Importance** Our response and remission results (73% and 55% respectively) are overall higher than most of those reported in the literature with depressed patients of similar duration, treatment resistance, and severity and demonstrate the efficacy of combining intensive medication management with TMS. Though TMS and psychopharmacology have both been utilized alone or with minimal combinations for patients

with severe illness, the combination of TMS with intensive psychopharmacology is a novel concept that could potentially lead to greater response/remission rates and is worth exploring further.

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#### Learning Objectives:

- Discuss the efficacy of medication treatment, transcranial magnet stimulation (TMS), and the combination of intensive medication treatment with TMS for patients with TRD.
- Devise optimal treatment regimens for patients with treatment resistant major depressive disorders.

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#### **EDIVOXETINE AS ADJUNCTIVE TREATMENT FOR PATIENTS WITH MAJOR DEPRESSIVE DISORDER WHO ARE PARTIAL RESPONDERS TO SELECTIVE SEROTONIN REUPTAKE INHIBITOR TREATMENT: 3 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDIES**

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Eli Lilly and Company*

Objective: To present results from 3 studies (H9P-MC-LNBR, H9P-MC-LNBQ, and H9P-MC-LNBM) that assessed the efficacy and safety of the highly selective norepinephrine reuptake inhibitor (NRI), edivoxetine (EDX), compared to placebo (PBO) as adjunctive treatment for patients with major depressive disorder (MDD) who were partial responders to selective serotonin reuptake inhibitor (SSRI) treatment. Top-line efficacy and safety results, study methodology, and placebo response mitigation strategies will be discussed. Methods: Studies were 8-week acute, randomized, PBO-controlled, double-blind (DB), phase 3 clinical trials in patients with MDD who were partial responders to SSRIs. Study LNBR compared EDX (12–18 mg, once daily [QD]) + SSRI (n=230) with PBO+SSRI (n=219), Study LNBQ compared EDX (12–18 mg, QD) + SSRI (n=232) and EDX (6 mg, QD) + SSRI (n=226) with PBO+SSRI (n=231); and Study LNBM compared fixed-dose EDX (12 and 18 mg, QD) + SSRI (n=231 and n=230, respectively) with PBO+SSRI (n=240). All patients received adjunctive PBO for 3 weeks in a DB, PBO lead-in/confirmation of partial response phase. Patients were then randomized into an 8-week, DB adjunctive treatment phase, if they had <25% improvement (during confirmation) on Montgomery-Asberg Depression Rating Scale (MADRS) total and a MADRS total score  $\geq 14$ ; patients not randomized remained on adjunctive PBO. The primary outcome was mean change from baseline to week 8 in MADRS total score. Key secondary efficacy measures included Sheehan Disability Scale, remission rates (MADRS total score  $\leq 10$ ), and Hospital Anxiety and Depression Scale scores. Changes in efficacy measures were analyzed using repeated measures analysis. Placebo response mitigation strategies included blinding of randomization criteria,

timing of randomization, use of a DB, PBO lead-in phase, centralized rating at study entry, and rigorous training and calibration of site-raters for MADRS. Results: Each trial failed to meet the primary and most secondary endpoints. The least-squares mean changes in MADRS total score were Study LNBR: -8.73 (EDX 12–18 mg + SSRI) and -8.49 (PBO+SSRI); Study LNBQ: -9.36 (EDX 12–18 mg + SSRI), -9.59 (EDX 6 mg + SSRI), and -9.36 (PBO+SSRI); Study LNBQ: -8.47 (EDX 12 mg + SSRI), -8.70 (EDX 18 mg + SSRI), and -7.77 (PBO+SSRI). Edivoxetine was generally well-tolerated with adverse events (AEs) consistent with a noradrenergic mechanism of action. Discontinuation due to AEs was generally low across studies (2.7%–6.5% in adjunctive EDX groups; 2.2%–3.7% in adjunctive PBO groups). Mean increases in blood pressure and pulse and mean decreases in weight were observed in all adjunctive EDX+SSRI groups. Conclusions: Within the context of the above study design methodologies, administration of adjunctive edivoxetine to patients with MDD who were partial responders to SSRIs did not significantly improve outcomes on the primary and most secondary measures when compared to adjunctive placebo.

### **Learning Objectives:**

- Describe recent study results examining efficacy of the highly selective NRI reuptake inhibitor, EDX, compared to PBO as an adjunctive treatment for patients with MDD who were partial responders to SSRIs.
- Discuss strategies used to improve signal detection in clinical trials of MDD.

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## **EFFECTS OF VILAZODONE ON SEXUAL DYSFUNCTION IN MAJOR DEPRESSIVE DISORDER: A RANDOMIZED, DOUBLE-BLIND TRIAL WITH PLACEBO AND ACTIVE CONTROLS**

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Introduction: Vilazodone, a serotonin reuptake inhibitor and 5-HT<sub>1A</sub> receptor partial agonist, is approved for the treatment of major depressive disorder (MDD) in adults. A recent positive Phase IV study (NCT01473394) supported the efficacy of vilazodone 20 and 40 mg/day (VLZ 20, VLZ 40) in the treatment of MDD; citalopram 40 mg/day (CIT) was used to evaluate assay sensitivity. All active treatment groups showed statistically significant improvement versus placebo (PBO) on the Montgomery-Asberg Depression Rating Scale (MADRS), the primary efficacy measure. Both MDD and treatment with serotonergic antidepressants can be associated with sexual dysfunction. Post hoc analyses characterized sexual functioning in patients with MDD treated with PBO, VLZ 20, VLZ 40, or CIT. Methods: A 10-week multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose study compared VLZ 20, VLZ 40, and CIT with PBO (NCT01473381). The study comprised male and female outpatients aged 18 to 70 years who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD and had a baseline MADRS score  $\geq 26$ . Sexual functioning was assessed using the Changes in Sexual Functioning Questionnaire (CSFQ) in 1147 patients (PBO=264, VLZ 20=267, VLZ 40=259, CIT=257) with a baseline and  $\geq 1$  postbaseline CSFQ score. Sexual dysfunction was defined as CSFQ scores  $\leq 47$  for men and  $\leq 41$  for women. Post hoc analyses evaluated mean change in CSFQ score from baseline to end of treatment (EOT). The percentage of patients with normal sexual function at baseline who met sexual dysfunction criteria at 2 consecutive double-blind visits and the percentage with sexual dysfunction at baseline who had normal sexual function at EOT were also analyzed. Results: A

high percentage of patients in all treatment groups had baseline sexual dysfunction: men (PBO=50%, VLZ 20=54%, VLZ 40=55%, CIT=52%); women (PBO=62%, VLZ 20=64%, VLZ 40=70%, CIT 67%). Baseline CSFQ scores were approximately 42 for all treatment groups. Least squares mean increase in CSFQ scores at EOT was 2.5 for PBO, 2.6 for VLZ 20, 2.0 for VLZ 40, 1.5 for CIT. In patients with normal baseline sexual function, 12% of PBO and 16%, 15%, and 17% of VLZ 20, VLZ 40, and CIT patients, respectively, met criteria for sexual dysfunction at 2 consecutive double-blind visits. In patients with baseline sexual dysfunction, 33% of PBO, and 35%, 30%, and 28% of VLZ 20, VLZ 40, and CIT patients improved to normal sexual function at EOT. Conclusions: In a post hoc analysis of a Phase IV trial, the rates of sexual dysfunction were similar for PBO-, VLZ-, and CIT-treated patients. Mean CFSQ scores increased in all treatment groups, however, CFSQ score increases were numerically greater in both VLZ groups compared with CIT.

### **Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the effects of vilazodone and citalopram treatment on sexual function in patients with MDD.
- At the conclusion of this session, the participant should be able to 2 understand effects of vilazodone on patients with normal baseline sexual function and with baseline sexual dysfunction.

**Source of Funding:** Supported by Forest Laboratories, Inc.

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### **DO THE DISSOCIATIVE SIDE EFFECTS OF KETAMINE MEDIATE ITS ANTIDEPRESSANT EFFECTS?**

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Background: The N-methyl-D-aspartate receptor antagonist ketamine has rapid antidepressant effects in major depression. Psychotic-like symptoms and hemodynamic changes are known side effects of ketamine, but it is unclear if these side effects relate to its antidepressant efficacy.

Methods: Data from 108 treatment-resistant inpatients meeting criteria for major depressive disorder and bipolar disorder who received a single subanesthetic ketamine infusion were analyzed. Pearson correlations were performed to examine potential associations between rapid changes in dissociation and psychotic-like experiences with the Clinician-Administered Dissociative States Scale (CADSS), Brief Positive Rating Scale (BPRS), respectively, manic symptoms with Young Mania Rating Scale (YMRS), and vital sign changes with percent change in the 17-item Hamilton Depression Rating Scale's (HDRS) at 40 and 230 minutes and days 1 and 7. Results: Pearson correlations showed significant association between increased CADSS score at 40 minutes and percent improvement with ketamine in HDRS at 230 minutes ( $r=-0.35$ ,  $p=0.007$ ) and Day 7 ( $r=-0.41$ ,  $p=0.01$ ). Changes in YMRS or BPRS Positive Symptom score at 40 minutes were not significantly correlated with percent HDRS improvement at any time point with ketamine. Changes in systolic blood pressure, diastolic blood pressure, and pulse were also not significantly related to HDRS change. Limitations: Secondary data analysis, combined diagnostic groups, potential un-blinding. Conclusions: Among the examined mediators of ketamine's antidepressant response, only dissociative side effects predicted a more robust and

sustained antidepressant. Prospective, mechanistic investigations are critically needed to understand why intra-infusion dissociation correlates with a more robust antidepressant efficacy of ketamine.

### **Learning Objectives:**

- Learn about the potential association between ketamine's antidepressant efficacy and neuropsychiatric side effects, e.g. dissociation and psychotomimetic effects.
- Learn about the potential association between ketamine's antidepressant efficacy and vital sign changes.

**Source of Funding:** Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH), by a NARSAD Independent Investigator Award to CAZ, and by the Brain & Behavior Mood Disorders Research Award to CAZ.

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### **IN MDD PATIENTS SWITCHED AFTER AN INADEQUATE RESPONSE, THE EFFICACY AND TOLERABILITY OF VORTIOXETINE VERSUS AGOMELATINE IS INDEPENDENT OF PREVIOUS ANTIDEPRESSANT TREATMENT**

*George I. Papakostas<sup>1</sup>, Rebecca Z. Nielsen<sup>2</sup>, Marianne Dragheim<sup>2</sup>*

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**Objective:** Vortioxetine was shown to be superior to agomelatine in a study in adult patients with major depressive disorder (MDD) who had an inadequate response to SSRI/SNRI monotherapy and therefore wished to switch treatment [1]. This analysis investigated if the efficacy and tolerability of vortioxetine treatment was independent of the previous SSRI/SNRI treatment.

**Methods:** This was a double-blind, randomized, 12-week comparator study where patients were randomized (1:1) to vortioxetine (10-20 mg/day) or agomelatine (25-50 mg/day) [2]. The primary efficacy endpoint was the change from baseline to Week 8 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score in the full-analysis set (FAS) analysed by MMRM. The ANCOVA, LOCF was conducted as a sensitivity analysis. The analyses were repeated in subgroups (SSRI/SNRI) based on the previous antidepressant that had inadequately treated the current MDE. **Results:** On the pre-defined primary efficacy endpoint (overall study population), vortioxetine (n=252) was statistically significantly superior to agomelatine (n=241) by -2.2 (95% CI: -3.5 to -0.8; p<0.01) MADRS points. Approximately 76% (n=189 [vortioxetine], n=188 [agomelatine]) were previously treated with an SSRI (citalopram, escitalopram, paroxetine, or sertraline) or 23% (n=62 [vortioxetine], n=52 [agomelatine]) with an SNRI (duloxetine or venlafaxine). The baseline characteristics were similar in all subgroups including a mean MADRS total score of approximately 29. The differences between vortioxetine and agomelatine at Week 8 on MADRS total score (FAS, MMRM) was -2.6 (n=164 [vortioxetine], n=150 [agomelatine]) (p<0.01) for patients switching from an SSRI and -1.8 (n=56 [vortioxetine], n=40 [agomelatine]) (ns) for patients switching from an SNRI. Similar results were seen at Week 12, and analysed by ANCOVA, LOCF, as well as these analyses repeated in the subgroups based on the 6 individual previous SSRI or SNRIs. Withdrawal rate and incidence of adverse events (AEs) were similar in the overall study population and in the 2 subgroups regardless of the previous SSRI or SNRI treatment. Comparing vortioxetine and agomelatine in the following 3 groups: overall study population, previously SSRI or SNRI treated, the withdrawal rate was 21% vs 26%, 21% vs 25% and 21% vs 28%, respectively; and

AE incidence was 54% vs 53%, 56% vs 53%, and 50% vs 51%, respectively. Nausea was the most common AE in the vortioxetine group. Conclusions: Vortioxetine is superior to agomelatine in the treatment of patients with MDD who had an inadequate response to a single course of SSRI or SNRI monotherapy and is equally well tolerated. The advantage is independent of any of the 6 previous treatments, both divided into class and individually. The results of the subgroup analyses support the advantage of switching inadequate responders to vortioxetine.

#### References:

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#### Learning Objectives:

- To understand the effects of switching adult patients with MDD with an inadequate response to an SSRI or an SNRI to vortioxetine 10-20mg or agomelatine 25-50mg on depressive symptoms.
- To understand the effects of switching adult patients with MDD to vortioxetine 10-20mg or agomelatine 25-50mg on tolerability.

**Source of Funding:** This study was sponsored by H. Lundbeck A/S.

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#### **ADJUNCTIVE LANICEMINE (AZD6765) IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND A HISTORY OF INADEQUATE RESPONSE TO ANTIDEPRESSANTS: PRIMARY RESULTS FROM A RANDOMIZED, PLACEBO-CONTROLLED STUDY (PURSUIT)**

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**Objective:** In a previous Phase IIb study, adjunctive lanicemine (100 mg or 150 mg, 3 intravenous infusions/week), a low-trapping NMDA channel blocker, was associated with significantly greater change in MADRS score at Week 3 versus placebo in patients with MDD and history of inadequate response to antidepressants (LS mean change -13.4, -12.7, and -7.9 respectively; P=0.006 and 0.019 vs placebo; n=152). (1) This Phase IIb study investigated the efficacy and tolerability of adjunctive lanicemine over 12 weeks, with 2-week follow-up (Study 31 [PURSUIT]; NCT01482221). **Methods:** A 49-center, 4-country, randomized, parallel-arm, double-blind, placebo-controlled study of adjunctive lanicemine in 2 dose groups (50 mg or 100 mg/infusion) in patients with MDD and history of inadequate response to  $\geq 3$  antidepressants. Lanicemine or placebo (saline) was infused 3 times a week in Weeks 1-3, once a week in Weeks 4-6, and once every 2 weeks in Weeks 7-12. Background psychoactive medications were maintained at same doses. Primary efficacy variable was change in MADRS score at Week 6 by ITT analysis. **Results:** 302 patients were randomized; 78.8% completed the study, including follow-up. LS mean change in MADRS score at 6 weeks was -14.4 for lanicemine 50 mg, -14.4 for lanicemine 100 mg, and -13.2 for placebo (lanicemine groups: NS versus placebo).

Lanicemine groups did not differ significantly from placebo in secondary efficacy variables, including response rate (MADRS score reduction  $\geq 50\%$  at Week 6: 36.0%, lanicemine 50 mg; 44.0%, lanicemine 100 mg; 39.0%, placebo). Adjunctive lanicemine was generally well tolerated. Adverse events (AEs)  $\geq 1$  were reported by 77.1% and 70.0% patients in lanicemine and placebo groups, respectively. More patients in the lanicemine 100 mg group (8.9%) discontinued treatment due to AE than in lanicemine 50 mg (2.0%) and placebo groups (4.0%). Dizziness was the most common AE (26.7%, lanicemine 50 mg; 45.0%, lanicemine 100 mg; vs 10.0%, placebo). There were no clinically meaningful differences between lanicemine and placebo groups in psychotomimetic AEs or dissociative symptoms. Discussion: Adjunctive lanicemine (50 mg or 100 mg/infusion) with a tapering frequency of infusions was not superior to placebo in reducing depressive symptoms in patients with MDD and inadequate response to prior antidepressants. Potential explanations for the disparity between this study and a previous adjunctive Phase IIb study (1) are explored in post-hoc analyses.

#### Literature References:

- Sanacora G, Smith MA, Pathak S, et al. Mol Psychiatry. 2013 Oct 15. [Epub ahead of print]
- Pathak S, Su H-L, Posener J et al. Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and a history of inadequate response to antidepressants: post-hoc analyses of a randomized, placebo controlled study (PURSUIT). Abstract submission to ASCP 2014.

#### Learning Objectives:

- Understand the outcomes of a second Phase IIb study investigating the efficacy and tolerability of adjunctive lanicemine in patients with MDD.
- Compare the outcomes of the first and second Phase IIb studies of adjunctive lanicemine in MDD.

**Source of Funding:** AstraZeneca.

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#### IMPACT OF A CULTURALLY-FOCUSED PSYCHIATRIC CONSULTATION ON DEPRESSIVE SYMPTOMS AMONG SPANISH- AND ENGLISH-SPEAKING LATINOS IN PRIMARY CARE

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**Objective:** We implemented a culturally-focused psychiatric (CFP) consultation service to increase engagement in mental health care and reduce depressive symptoms among adult Latino primary care patients. The current aim was to compare the efficacy of the CFP service to reduce depressive symptoms in primarily Spanish-speaking Latino patients as compared to English-speaking Latino patients. **Methods:** In a randomized controlled study design, primary care provider (PCP) clinics were randomly selected to provide either the two-session CFP intervention or enhanced usual care. For participants in the CFP arm, study clinicians

(psychiatrists, psychologists) provided a culturally-tailored psychiatric assessment, psychoeducation, cognitive-behavioral tools and tailored treatment recommendations; PCPs were provided a consultation summary. Depressive symptoms (as measured by the Quick Inventory of Depressive Symptoms, Self-Rated, QIDS-SR) were assessed at baseline and six-month follow-up. Multiple regression analysis was conducted to evaluate whether Spanish-speaking versus English-speaking CFP participants showed greater improvement in depressive symptoms at follow-up, controlling for baseline QIDS-SR scores and significant co-variables. Results: The majority of participants (n=118) were Spanish speakers (64.4%). The final multiple regression model indicated that CFP participation predicted lower depressive symptoms at follow-up (unstandardized beta -3.07,  $t=-3.067$ ,  $p=.003$ ), independent of baseline depressive symptoms, age, gender, and primary language status (unstandardized beta 1.111,  $t=-1.030$ ,  $p=.306$ ). Conclusions: Current results suggest that both Spanish-speaking and English-speaking Latinos experiencing depressive symptoms may benefit from a short-term culturally focused psychiatric consultation, regardless of primary language spoken. Findings also support the need for integration of psychiatric interventions for Latinos with depression in the primary care setting.

### **Learning Objectives:**

- Participants will be able to list at least three important factors to consider when treating minority patients with depression.
- Participants will be able to describe the role of linguistic and cultural issues in a cultural assessment for depression.

**Source of Funding:** The Robert Wood Johnson Foundation

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### **ASSOCIATION BETWEEN PHYSICIANS' EXPECTATIONS AND CLINICAL RESPONSE: RE-ANALYSIS OF DATA FROM THE HYPERICUM DEPRESSION TRIAL STUDY GROUP**

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**Background:** We have previously shown an association between patient belief and treatment response in the Hypericum Depression Trial Study Group's 2002 study. We re-examined these data to determine whether clinical improvement was associated with physician belief about assigned therapy. **Methods:** 340 adults with major depression and baseline scores  $\geq 20$  on the 17-item Hamilton Depression Scale (HDRS-17) were randomized to Hypericum 900-1500 mg/d, sertraline 50-100 mg/d, or placebo for 8 weeks. At week 8, physicians guessed their patients' treatment. We analyzed 238 subjects with at least one post-baseline visit and physician guess data. Univariate ANOVA examined association between guess and improvement. Logistic regression examined whether treatment assignment moderated the effect of belief on response ( $\geq 50\%$  decrease in HDRS-17 score) and remission (final HDRS-17 score  $< 8$ ). **Results:** Patient and doctor guesses agreed at 56% for sertraline, 68% for Hypericum, and 55% for placebo ( $p < 0.001$  for all). Doctors guessed placebo correctly (34%) more than sertraline (22%) or Hypericum (17%); comparisons reached significance for guessing Hypericum versus placebo ( $p = 0.011$ ) or an active treatment (sertraline or Hypericum) versus placebo ( $p < 0.001$ ). Doctors'



guess was significantly associated with clinical improvement and response ( $p < 0.001$  for both). Response rate comparisons between guess groups were significant for Hypericum ( $p < 0.001$ ) and sertraline ( $p < 0.001$ ) versus placebo but not for sertraline versus Hypericum. Conclusion: Doctors' guesses were associated with degree of improvement, but may be influenced more by symptomatic improvement or side effects than by pre-existing beliefs. Results show association but not causation.

**Source of Funding:** Parent study grant number: N01 MH070007 Parent study ClinicalTrials.gov Identifier: NCT00005013

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### **A CASE MIX SEVERITY INDEX FOR DEPRESSION**

*Mark Zimmerman*

*Rhode Island Hospital*

**Introduction:** Throughout medicine, there has been increasing interest in comparing the relative effectiveness of alternative treatments in routine clinical practice, and comparing the effectiveness of clinicians and clinical programs. However, efforts to compare health care delivery systems or individual practitioners in the outcomes they achieve are typically met with concerns that samples differ at baseline in their likelihood of achieving good or negative outcomes. The usual approach towards addressing for such baseline differences is to develop indices of case mix severity and adjust for differences in risk. In the present report from the Rhode Island MIDAS project we describe the development of a measure a case mix severity for depression (CMS-D). **Methods:** One hundred fifty three depressed patients who presented for treatment, or who were in ongoing treatment and had their medication changed, were evaluated at baseline and at 4 month follow-up. In addition to the CMS-D, the patients were rated on 17-item Hamilton Rating Scale for Depression (HAM-D) and Montgomery-Asberg Depression Rating Scale. At follow-up the patients also indicated if they considered themselves to be in remission. **Results:** On each outcome measure, patients who were in remission scored higher on the CMS-D scale than the patients who were not in remission. Subdividing patients into quartiles on the CMS-D, the mean remission rate across all measures declined in each successive quartile (57.3%, 41.2%, 33.8%, 18.8%). **Discussion:** The CMS-D was significantly predictive of outcome

of the treatment of depression in routine clinical practice. The utility of such a scale in treatment outcome studies, and efforts to link reimbursement to clinical outcomes will be discussed.

**Learning Objectives:**

- At the conclusion of this presentation the participant should become familiar with the concept of case-mix severity.
- At the conclusion of this presentation the participant should become familiar the reliability and validity of a measure of case-mix severity that predicts remission from depression.

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**HOW MANY DIFFERENT WAYS DO PATIENTS MEET THE DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER?**

*Mark Zimmerman*

*Rhode Island Hospital*

Introduction: The DSM-5 approach towards defining major depressive disorder (MDD), based on a minimum number of features from a longer list, results in heterogeneity in patients' clinical profile because there are many different combinations of criteria that qualify for a diagnosis. Altogether, there are 227 possible ways to meet the symptom criteria for MDD. However, symptom occurrence is not random, and some symptoms co-occur significantly beyond chance. This raises the questions of whether all of the theoretically possible different ways of meeting the MDD criteria actually occur in patients, and whether some combinations of criteria are much more common than others. Methods: The focus of the present report is the 1,566 patients who met DSM-IV criteria for MDD at the time of the evaluation and who were interviewed with semi-structured interviews. Results: If each of the 227 possible combinations of criteria were equally likely to occur then approximately 0.4% (or 7 patients) would meet each combination. The patients met the MDD symptom criteria in 170 different ways. Put another way, one-quarter (57/227) of the criteria combinations did not occur. The most frequent combination was the presence of all 9 criteria (10.1%, n=157). Nine combinations (all 9 criteria, three of the 8-criterion combinations, 4 of the 7-criterion combinations, and one 6-criterion combination) were present in more than 2% of the patients, together accounting for more than 40% of the diagnoses. Discussion: The polythetic definition of MDD, which requires a minimum number of criteria from a list, results in significant diagnostic heterogeneity because there are many different ways to meet criteria. While there is significant heterogeneity amongst patients meeting the MDD diagnostic criteria, a relatively small number of combinations could be considered as diagnostic prototypes as they account for more than 40% of the patients diagnosed with MDD.

**Learning Objectives:**

- At the conclusion of this presentation the participant will become familiar with the number of ways it is possible to meet the diagnostic criteria for major depressive disorder.
- At the conclusion of this presentation the participant will become familiar with the most frequent criteria combinations met for major depressive disorder and how many criteria combinations were not met in a large cohort of patients.

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## **RANDOMIZED CONTROLLED SAFETY AND EFFICACY TRIALS OF LISDEXAMFETAMINE DIMESYLATE FOR ADULTS WITH MODERATE TO SEVERE BINGE EATING DISORDER**

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Objective: Binge eating disorder (BED) episodes of excessive eating are associated with a sense of loss of control that may involve dopaminergic (DA) and noradrenergic (NE) dysfunction.

Lisdexamfetamine dimesylate (LDX), which modulates DA and NE systems, may reduce binge eating frequency in BED. Method: Two identically designed, multicenter, randomized, double-blind, placebo-controlled trials enrolled adults meeting DSM-IV-TR™ criteria for BED.

Participants were assigned randomly 1:1 for optimal dose titration to placebo or LDX (50 or 70 mg/d), with optimized dose maintained to the end of double-blind phase (week 12 or early termination [ET]). Efficacy and safety were evaluated at each visit, and safety again at a 1-week poststudy follow-up. Primary efficacy endpoint, change from baseline in binge eating days/week at weeks 11/12, was assessed with mixed-effects models for repeated measures over all postbaseline visits. Key secondary endpoints included 4-week binge eating cessation at week 12/ET and dichotomized Clinical Global Impressions-Improvement (CGI-I) 7-point scale (“very much improved”/ “much improved” vs “minimally improved” to “very much worse”). Safety was evaluated with treatment-emergent adverse events (TEAEs) and vital sign measures (including weight). Results: Study 1 enrolled 383 and study 2 enrolled 390 participants (safety populations, 379 [86.5% female] and 366 [85.2% female], respectively; full-analysis populations, 374 and 350, respectively). In study 1, LS mean (SEM) changes from baseline in binge eating days/week at week 11/12 were -2.51 (0.125) and -3.87 (0.124), placebo and LDX, respectively; in study 2, -2.26 (0.137) and -3.92 (0.135), placebo and LDX, respectively (P<0.001 for each). For placebo and LDX, respectively, percent of participants improved on CGI-I scores at week 12/ET in study 1 were 47.3% and 82.1%; in study 2, 42.9% and 86.2%, (P<0.001 for each). For study 1, 14.1% and 40.0% for placebo and LDX, respectively reached 4-week cessation at week 12/ET, as did 13.1% and 36.2% of placebo and LDX, respectively, in study 2 (P<0.001 for each). Reported TEAEs in ≥10% of LDX participants were dry mouth, insomnia, and headache in both studies. Serious TEAEs were reported in 2 (1.1%) placebo participants in each study and in 3 (1.6%) and 1 (0.6%) LDX participants in study 1 and study 2, respectively. Severe TEAEs occurred in 6 (3.2%) placebo participants in each study and 17 (8.9%) and 7 (3.9%) LDX participants in study 1 and study 2, respectively. Mean changes in pulse and blood pressure in both studies were consistent with known effects of LDX.

Discontinuations for TEAEs included 5 (2.7%) placebo and 12 (6.3%) LDX participants in study 1; 4 (2.2%) placebo and 7 (3.9%) LDX participants in study 2. Conclusions: LDX at optimized doses of 50 and 70 mg/d demonstrated significant improvement in reduction of binge eating days/week and producing a significantly higher proportion CGI-I improvement and 4-week binge eating cessation versus placebo. Safety profile is generally consistent with known safety profile of LDX in adults with ADHD. Learning Objectives: In 2 identically designed clinical trials, LDX 1. Appeared superior to placebo in decreasing binge eating disorder behavior 2. Had no unexpected safety signals

## **PRAZOSIN FOR NIGHTMARES IN PATIENTS WITH EATING DISORDERS: A CASE SERIES**

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*<sup>1</sup>Einstein Medical Center, <sup>2</sup>Belmont Center Comprehensive Treatment*

**Introduction:** Prazosin is a centrally active alpha-1 adrenergic receptor antagonist, traditionally used to treat hypertension and benign prostatic hyperplasia. It has been found in placebo-controlled studies to reduce trauma nightmares and overall severity of symptoms in patients with combat and civilian related post-traumatic stress disorder (PTSD). Several studies have shown a high comorbidity between eating disorders and PTSD and about 60% of patients with eating disorder have experienced at least one trauma in their life. Prazosin for nightmares has not been studied in eating disorder sub-group of populations, who have an increased risk of side effects due to increased risk of electrolyte disturbances and hemodynamic compromise. In this case series, we present series of 4 women diagnosed with eating disorder with distressing nightmares who were treated successfully with Prazosin. **Method** We conducted a retrospective chart review of patients who were started on prazosin for nightmares on the eating disorder unit. Four patients with diagnosis of eating disorder and history of trauma were selected and these charts were reviewed in detail for co-morbid axis 1 diagnosis, past psychiatric history, social history and progress on the unit while on prazosin. **Discussion** Although there have been no studies about use of prazosin in patients with eating disorders, this case series illustrates that prazosin appears to be effective in treating trauma nightmares in these patients. Though orthostatic hypotension has been reported with prazosin, eating disorder patients appear to be more susceptible, as three out of our four cases presented with this event. This series also suggests that sexual trauma is more common in patients with eating disorder, as three of our four cases had sexually related trauma that manifested as nightmares. The intensity of the nightmares was independent of the nature of the trauma or intensity of the eating disorder and mood symptoms. All patients reported reduction in nightmares within two weeks of therapy. The limitations of this case series were that there were no men included, there were no patients with the diagnosis of bulimia and none of the patients had any major medical co-morbidities. More research is warranted in this area given the increased prevalence of trauma and nightmares in this population.

### **Learning Objectives:**

- To summarize the efficacy and side effects of prazosin to treat trauma-related nightmares in patients with eating disorders.
- To emphasize close monitoring and appropriate dosing of prazosin in susceptible population of patients with co-morbid conditions and polypharmacy.

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## **EFFECTS OF SCOPOLAMINE ON WORKING MEMORY TASK AND RESTING FUNCTIONAL CONNECTIVITY USING FMRI IN HEALTHY KOREAN SUBJECTS**

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**Introduction:** Cholinergic neurons are widely distributed throughout the CNS and have been implicated in regulating diverse behaviors including memory, attention, arousal and sleep. The major cholinergic projections within the CNS include the basal forebrain, consisting of nuclei in the medial septum (MS) and nucleus basalis of Meynert which project to the cortex and amygdala, and posterior brainstem nuclei consisting of pedunculopontine tegmental nucleus and

lateral dorsal tegmental nuclei which in turn project to the thalamus, reticular formation and ventral tegmental area. Basal forebrain cholinergic nuclei signaling through muscarinic and nicotinic-acetylcholine receptors are believed to play a role in mediating attention and cognitive function. Scopolamine, a non-selective muscarinic antagonist, has been demonstrated to impair working memory and attention in animal and human studies. Few studies have examined the impact of scopolamine on neural correlates of specific cognitive domains using functional MRI (fMRI). While these studies have demonstrated alterations in activation of specific brain regions associated with episodic, spatial and working memory, few human trials have examined the effect of scopolamine on resting state networks. Methods: Ten healthy male and female Korean subjects participated in a randomized, double-blind, placebo-controlled, cross-over, single-dose, outpatient study to investigate the effects of scopolamine on working memory load and resting state functional connectivity using fMRI. While data do not support differences in scopolamine pharmacokinetic or pharmacodynamic effects between Asians and non-Asian populations, there are reports of environmental factors such as diet and lifestyle impacting pharmacodynamic effects in this population. Upon completion of screening procedures and providing informed consent, subjects were randomized to receive scopolamine (0.5 mg) or placebo (saline) administered subcutaneously under fasted conditions. The scopolamine dose was selected based upon previously published reports examining the dose-response effects on disruption of memory without promoting significant sedation effects. Based upon known pharmacokinetic properties of scopolamine, scopolamine (or placebo) was administered 90 min prior to initiating functional MRI scanning protocol. A Siemens 3 Tesla Verio scanner, with a 32-channel head coil was used for all fMRI procedures. EPI-BOLD scans were conducted during both the resting state and cognitive challenges using a previously established version of the n-back paradigm. Briefly, the task consisted of a block design with three conditions, which were each presented three times in a pseudorandomized fashion. Each condition involved four occurrences of a single, prespecified target in a string of letters that were presented sequentially in a pseudorandomized fashion on a gray background. Subjects were asked to press a single button using their right index finger whenever the target appeared. Each condition was preceded by a written instruction for 10s, which indicated the target. Dosing and fMRI scanning procedures were conducted over 2 separate clinic days for each subject within each dosing cohort (Group A and Group B) separated by a 2 week washout. Additionally, subjects were administered the Visual Analogue Scales at baseline (1 hr predose) and 3 hrs postdose. Results/Conclusions: Results and conclusions will be presented at the ASCP Meeting.

### **Learning Objectives:**

- Develop additional skills in utilizing MRI as a translational biomarker in evaluating novel neuropsychiatric compounds in early phase trials.
- Develop expertise in the utilization of novel functional MRI paradigms in combination with translational methodologies to include cognitive stimulus tasks and simultaneous EEG recording.

**Source of Funding:** This study was an internally funded study by PAREXEL International.

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**Introduction:** The current situation regarding the teaching of psychopharmacology is complicated secondary to 1) decreased funding for psychiatric education in general and specifically with marked decreases of industry support, 2) increased neuroscience and clinical articles as well as the number of journals including print and web have increased, 3) decreased reading by students and there is a sharply decreased number of published texts, 4) increased emphasis on teaching psychotherapy and requirements to teach ‘non-clinical’ competencies, such as systems-based learning, often come at the expense of curricular time for psychopharmacology, 5) decreased numbers of academics who have the expertise and time to teach psychopharmacology and finally 6) strong anti-industry and anti-drug treatment biases in the fields. **Methods:** Over the past two decades, we have done follow-up surveys of users and programs of the psychopharmacology curriculums for both the medical students and psychiatric residents. **Results:** Many programs were unaware of the existence of these teaching tools. The time required for teaching and the potential costs were key barriers to utilization. Where the curriculums were purchased; they were used – either as a whole or in part – depending on the size of the program. They were judged to be very effective in improving learning. There were strong biases and prohibitions to communicating the existence of the teaching tools e.g. teachers could not use their organizational list-serves to let their teaching colleagues know of recent updates. **Conclusion:** The teaching and learning of cutting-edge medical student and psychiatric resident’s psychopharmacology has become increasingly challenging. Novel and creative approaches to prepare and reward faculty to teach, and motivate students to learn, the intricacies of psychopharmacologic management are needed.

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## **IS PAIN A RISK FACTOR FOR SUICIDALITY AS ASSESSED BY THE C-SSRS AND S-STIS? FINDINGS FROM AN ADULT INPATIENT PSYCHIATRIC SAMPLE**

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**Introduction:** There is an urgent need to identify risk factors for suicidal ideation and behavior. A literature review found an increased risk for suicidality among chronic pain patients compared to the general population; a relationship may also exist between pain severity and suicidality (1). Utilizing two standardized suicide assessment instruments, the current study examined the relationship between pain and suicidality in a sample of adult psychiatric inpatients. **Method:** Data were collected and analyzed as part of an original study comparing suicide assessment instruments in adult psychiatric inpatients (n = 199). Complete medical record data were available for 86.9% of patient participants (n = 173). Patients rated their current pain on a scale of 0 (no pain) to 10 (unbearable pain) as part of the intake pain assessment. During the study, patients completed a Risk Assessment Measure (RAM) which included a question about frequency of pain (Over the past month, have you had pain almost every day?). Patients also completed the Columbia Suicide Severity Rating Scale (C-SSRS) and Sheehan Suicidality Tracking Scale (S-STIS), which assessed past month suicidal ideation and behavior. **Analysis:** As part of a secondary analysis, ANOVAs tested for relationships between suicidality and pain severity (0 to 10). Chi-square tests tested for relationships between suicidality and presence of

pain (yes or no). Results: As a group, patients indicated a low level of current pain on the intake assessment ( $M = 3.17$ ,  $SD = 3.60$ ). Those reporting suicidal ideation or behavior on the C-SSRS and S-STS did not report a significantly higher amount of pain than those not reporting suicidal ideation or behavior ( $p's > .05$ ). On the RAM, 60.3% ( $n = 120$ ) of patients reported having pain almost every day over the past month. Patients experiencing pain were not more likely to report recent suicidal ideation or behavior on the C-SSRS or S-STS ( $p's > .05$ ). Discussion: Our data do not suggest links between pain severity or presence of pain and suicidality in adult psychiatric inpatients. The literature on pain severity and suicidality is conflicted (1). While some studies indicate a positive relationship between chronic pain and suicidality (2), others have found no relationship (3). Further studies are needed to address these discrepancies. The high percentage of psychiatric inpatients reporting frequent pain warrants further attention by clinicians.

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### Learning Objectives:

- Examine relationship between suicidality and pain in an inpatient psychiatric setting.
- Contribute to literature on risk factors for suicidality.

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### **A PROSPECTIVE OPEN-LABEL TRIAL OF MEMANTINE HYDROCHLORIDE FOR THE TREATMENT OF CORE FEATURES OF AUTISM SPECTRUM DISORDER IN HIGH-FUNCTIONING ADULTS**

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Treatment studies for the management of core features of autism spectrum disorder (ASD) are limited. There is a growing body of evidence demonstrating patterns of glutamate dysregulation in ASD. Our group recently examined adolescents with ASD using spectroscopic neuroimaging and found increased glutamate levels in the anterior cingulate cortex, a brain region that regulates the interaction of cognitive and affective processes [1]. Some research suggests that glutamate modulation could have effects on ASD. Memantine hydrochloride is an N-methyl-D-aspartate (NMDA) receptor antagonist approved by the FDA for the treatment of moderate to severe Alzheimer's disease and has been associated with improvement in attention-deficit/hyperactivity disorder (ADHD) symptoms and cognitive performance in adults with ADHD [2]. This study evaluated memantine hydrochloride as a treatment for core impairments of ASD in high-functioning adults. A 12-week, prospective, open-label trial was conducted to assess the effectiveness and tolerability of memantine hydrochloride for treating social and cognitive impairments in ASD and associated psychopathology (including ADHD, anxiety disorders and major depressive disorder [MDD]) in adults. Assessments included the Social Responsiveness Scale-Adult Research Version (SRS), Clinical Global Impression scale (CGI),

Behavior Rating Inventory of Executive Functioning-Adult Self Report (BRIEF), and Diagnostic Analysis of Nonverbal Accuracy 2 (DANVA2). Adverse events were assessed through collection of spontaneous self-reports, vital signs including weight, electrocardiograms, and hematological parameters. Eighteen high-functioning adults (mean IQ:  $107.6 \pm 15.3$ ) with at least moderately severe ASD (SRS total at entry:  $99.0 \pm 17.0$ ) were treated with memantine and 17 (94%) completed the trial. At study endpoint, the mean daily dose of memantine was  $19.7 \pm 1.2$  mg (range: 15-20 mg). Treatment with memantine was associated with statistically significant levels of improvement based on the mean SRS total score (endpoint:  $71.4 \pm 18.0$ ,  $p < 0.001$ ) and all SRS subscale scores at endpoint. Memantine treatment also resulted in significant improvement in the severity of ADHD (DSM ADHD Symptom Checklist baseline total:  $13.8 \pm 9.2$  vs. endpoint:  $7.9 \pm 5.9$ ,  $p < 0.001$ ) and executive functioning symptoms (BRIEF Global Executive Composite score:  $60.3 \pm 10.2$  vs.  $54.8 \pm 10.6$ ,  $p = 0.006$ ). On DANVA2 Faces, a test of subjects' ability to accurately read nonverbal emotional cues in faces, participants showed improvement with memantine treatment (mean number errors:  $6.1 \pm 2.7$  vs.  $4.9 \pm 2.5$ ,  $p \leq 0.001$ ). Treatment with memantine was generally well tolerated and was not associated with clinically significant change in cardiovascular or metabolic parameters. No serious adverse events were reported. Open-label memantine treatment appears to be beneficial in the treatment of ASD and associated conditions in high-functioning adults. Future placebo-controlled studies are warranted to confirm these findings.

### Learning Objectives:

- To explore the hypothesis of glutamate dysregulation in the etiology of autism spectrum disorder.
- To learn about the safety and efficacy of memantine hydrochloride as a treatment for core features of autism spectrum disorder based on data from a pilot open label trial.

**Source of Funding:** We wish to acknowledge the generous support of the Norma Fine Pediatric Psychopharmacology Fellowship Fund and the members of the MGH Pediatric Psychopharmacology Council.

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### THE EFFECT OF CITICOLINE SUPPLEMENTATION ON MOTOR SPEED AND ATTENTION IN ADOLESCENT MALES

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Background: Citicoline (CDP-choline; cytidine 5'-di-phosphocholine) is a nutraceutical marketed as a nutritional supplement in the United States. Citicoline supplementation has been related to a variety of cognitive enhancing effects in adults with neurological deficits, including improved performance on measures of executive function and attention. However, limited research has examined the effects of citicoline supplementation in healthy populations. Methods: Participants included 75 healthy adolescent males divided into treatment (n=51) and placebo groups (n=24). Participants completed a screening visit including a medical exam and clinical measures. Individuals were then randomly assigned to a 250 mg or 500 mg citicoline treatment group or placebo group. At Visit 1 (baseline) and Visit 3 (after 28 days of treatment or placebo),



participants completed measures of motor speed and attention. Specifically, participants completed the Finger Tap Test during which participants are required to press a lever as many times as possible during discrete time periods, and the Ruff 2&7 Selective Attention Test, a timed cancellation task in which participants cross out 2's and 7's embedded in blocks of distractor numbers or letters. Results: ANCOVAs were run to examine differences between treatment and placebo groups on Finger Tap Total Dominant Hand (FTDH) and Ruff 2&7 Speed task at Visit 3. Visit 1 performances (FTDH and Ruff 2&7 Speed respectively) were included as covariates to account for baseline performance. Between group differences showed that after 28 days of citicoline supplementation individuals in the treatment group exhibited increased motor speed compared to individuals in the placebo group ( $p = 0.03$ ; treatment group FTDH Visit 1 mean = 479.96, SD = 69.39; treatment group FTDH Visit 3 mean = 518.05, SD = 49.86; placebo group FTDH Visit 1 mean = 504.90, SD = 81.08; placebo group FTDH Visit 3 mean = 513.43, SD = 64.03). Additionally, individuals in the treatment group exhibited improved attention compared to the placebo group (Ruff 2&7 Speed  $p = 0.02$ ; treatment group Ruff Visit 1 mean = 86.98, SD = 22.62; treatment group Ruff Visit 3 mean = 104.90, SD = 21.31; placebo group Ruff Visit 1 mean = 84.04, SD = 16.93; placebo group Ruff Visit 3 mean = 96.79, SD = 19.56). Conclusion: Adolescents males who received 28 days of citicoline supplementation showed improved performance on measures of motor speed and attention compared to adolescent males who received placebo. These improvements may be mediated by a variety of brain regions including the anterior cingulate cortex, which has been implicated in motor and attention tasks.

### **Learning Objectives:**

The audience will be able to identify improvement in two cognitive domains subsequent to citicoline supplementation in adolescent males.

The audience will be able to discuss possible mechanisms by which these improvements occur.

**Source of Funding:** This study is supported by funds from KYOWA HAKKO BIO CO., LTD., Chiyoda-ku Tokyo, Japan

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## **EVALUATION OF THE IMPLEMENTATION OF PSYCHOTROPIC MEDICATION UTILIZATION PARAMETERS FOR CHILDREN AND ADOLESCENTS IN TEXAS FOSTER CARE**

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Background: In both the professional and lay press, increased attention has been devoted to the use of psychotropic medication in children. Foster children are a particularly vulnerable population that is often fraught with emotional distress and mental disorders; scrutiny has occurred regarding the use of psychotropic medication in these individuals. Methodologies improving the use of psychotropic medications in this population are needed. Methods: Subsequent to legislative action, the Texas Department of Family and Protective Services (DFPS) appointed a taskforce to develop psychotropic utilization parameters for foster children. The first edition of the parameters was published in 2005, with succeeding editions published in 2007, 2010, and 2013. These parameters were developed by a multidisciplinary taskforce with additional review and comment by relevant professional organizations and external reviewers.

While an evidence based approach was the goal of the respective taskforces, expert clinical consensus was used to fill in missing gaps of evidence in developing the prescribing parameters. These parameters were initially disseminated by DFPS, and then in 2008 a single mental health managed care organization implemented a system to utilize these parameters as a component of prospective quality of care assessment and clinician feedback for all foster children in Texas. Results: The use of one or more psychotropic medications in foster children decreased from 29.9% of children in FY 2004 to 19.3% in FY 2012. Within class polypharmacy decreased from 5% in FY 2004 to 1.7% in FY 2012. The percent of children receiving five or more psychotropic medications decreased from 1.4% in FY 2004 to 0.4% in FY 2012. The percent of children < 4 years of age receiving psychotropics decreased from 10.8% in FY 2004 to 3.6% in FY 2012. 2013 PARAMETERS: Major revisions included a decrease to 4 concomitant psychotropics for review of multidrug polypharmacy, the adoption of metabolic monitoring parameters, and updating and enhancement of dosing information. Conclusions: The implementation of state-wide psychotropic medication utilization parameters for foster children is associated with a decrease in the use of psychotropic medication and a decrease in polypharmacy. Prospective review and prescriber feedback improved utilization over dissemination and education alone. Children in foster care are a complex population with multiple factors contributing to emotional distress and the possibility of a mental disorder diagnosis. Although these interventions have resulted in a decrease in the use of psychotropic medication, additional efforts are needed to enhance the optimal care of mental disorders in foster children.

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#### Learning Objectives:

- Evaluate the effects of medication utilization parameters on medication use in an at risk population.
- Determine the effects of active monitoring and feedback versus parameters dissemination in changing prescribing behavior.

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#### HOW TO COLLABORATE WITH CRA, FROM A CHINA CLINICAL SITE PERSPECTIVE

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In the context of globalization, more and more international clinical studies of the psychotropic drugs have been performed. A growing number of multinational pharmaceutical companies introduce the early R&D of psychotropic drugs to China. Meanwhile, Chinese government has called for the development of critical pharmaceutical innovations and novel medical technologies, and announced new policies to fund such activities. So far, Pharmaceutical industry has achieved remarkable success in the innovation of psychotropic drugs in China. It is not a long history of clinical trial in China, which is about only 20 years. CRA in China has the same essential duties compare foreign colleagues when conducting his/her routine work in site, but besides, CRA in china has a lot of additional duties to smooth the procedure of clinical trial. I

will give you a typical clinical trial example to show what CRA may do and what site/CRC may do before site initiation, during site initiation, routine monitoring and close-out. I also share with you our experiences to establish CRA-CRC collaborating model in psychiatric hospital and the practice with Chinese characteristics. From CRA's aspect, there are some challenges to limit a good quality clinical trial. We also to know the primary background and current situation of CRA in China is quickly blooming pharmaceutical industry versus limited professionals, which is resulting in CRA declining generally, not only in local CRA or CROs, but also CRA from global pharmaceutical companies or CROs. I will share with you our strategies and experiences to resolve such issues, including overload, unqualified staff, insufficiency training, confused professional plan, etc.

### **Learning Objectives:**

- To learn brief history, current situation and trends of clinical trial in China.
- To understand China CRA-CRC collaborating model in psychiatric hospital and the practice with Chinese characteristics.

**Source of Funding:** China National Science and Technology Major Project for IND in psychiatry (2012ZX09303-003)

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### **TOLERABILITY AND SAFETY PROFILE OF ARIPIPRAZOLE ONCE-MONTHLY IN THE TREATMENT OF SCHIZOPHRENIA: A POOLED ANALYSIS FROM THE SAFETY DATABASE OF 11 COMPLETED OR ONGOING TRIALS**

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Background: Aripiprazole once-monthly (AOM), a long-acting injectable formulation of oral aripiprazole, is the first dopamine partial agonist available as a long-acting injectable formulation. In two pivotal trials of stable patients with schizophrenia (NCT 00705783, Kane et al. 2012; NCT 00706654, Fleischhacker et al. 2012), AOM delayed time to, and reduced the rate of impending relapse compared to placebo or a sub-therapeutic dose of AOM. Objectives: To report the overall long-term tolerability and safety profile of AOM. Methods: Data from the safety database of 11 completed or ongoing AOM trials in subjects with schizophrenia were used in this pooled analysis; 2 completed phase 3 trials (pivotal trials), 4 ongoing phase 3/3b trials (as of 02 April 2012 cut-off date), 4 completed phase 1/1b trials, 1 ongoing phase 1b trial. Exposure and treatment emergent adverse event (AE) data are summarized for AOM-400/300 mg, and the sub-therapeutic doses AOM-50/25mg. Results: A total of 1,539 subjects have been treated with AOM-400/300 mg and 168 have been treated with less than 300 mg/day (131/168 from the 25/50 mg arm of one pivotal trial). As of 02 April 2012, 995 subjects have received at least 7 aripiprazole injections (ie 6 months of exposure), 784 subjects at least 13 injections (ie 12 months of exposure), and 244 subjects at least 26 injections (ie 2 years of exposure). Treatment-emergent adverse events (TEAEs) resulted in trial discontinuation for 9.4% (145/1539) of AOM-400/300 mg treated subjects and 14.9% (25/168) of a subjects treated with less than 300. The TEAE reported for  $\geq 10\%$  of AOM-400/300 mg subjects was insomnia 11.0% (169/1539); TEAEs  $< 10\%$  to  $\geq 5\%$  of AOM-400/300 mg subjects) were headache (147/1539, 9.6%), anxiety

, 8.8% (136/1539), increased weight 7.7% (119/1539), nasopharyngitis 7.5% (115/1539), akathisia 7.1% (109/1539), injection site pain 7.0% (108/1539), and upper respiratory tract infection 5.5% (84/1539). The incidences of TEAEs were comparable with AOM<300 mg except for injection site pain (AOM-400/300 mg 7.0% (108/1539); AOM<300mg, 3.0% (5/168). The majority of TEAEs were either mild or moderate in severity. Conclusion: A substantial number of patients have been actively monitored for side effects after treatment with aripiprazole once-monthly for at least a year, and some for at least 2 years. Overall, the long-term tolerability and safety profile was consistent with the known safety profile of oral aripiprazole.

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- Fleischhacker et al. Aripiprazole once-monthly for the treatment of schizophrenia: a double-blind, randomized, non-inferiority study vs. oral aripiprazole. *Neuropsychopharmacology* 2012; 38, S339

#### Learning Objectives:

- To understand the long-term safety and tolerability profile of aripiprazole once-monthly in stabilized schizophrenia patients from a pooled analysis of the safety database.
- To determine the exposure of aripiprazole once-monthly in stabilized schizophrenia patients from a pooled analysis of the safety database.

**Source of Funding:** Supported by Otsuka Pharmaceutical Development & Commercialization, Inc., and H. Lundbeck A/S

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#### LEUCOCYTES POINT OF CARE MEASUREMENT IN CLOZAPINE THERAPY

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White blood cell monitoring, initially weekly, after week 18 (Europe) or 26 (USA) monthly, is obligatory in clozapine treatment, so patients are used to monthly venous blood sampling. Recently a point of care device for white blood cell count plus differentiation from capillary blood has become available. If shown to be acceptable to and preferred by the patients in question, it could form a breakthrough in blood sampling methods in clozapine maintenance therapy. Methods: Patients on clozapine maintenance therapy were asked to participate. In order to tap patient's attitude and preferences for one method, we developed a visual analogue scale ranging from 1-10. Results: 32 outpatients, 22 inpatients in a forensic clinic and 15 patients in a residential high care clinic agreed to give their informed consent. Outcome: no patients preferred venous blood sampling. Patients were either indifferent to the blood sampling method or they preferred capillary blood sampling. Conclusion: Capillary blood sampling in clozapine maintenance therapy is feasible and, so far as patients express a preference, preferred by the patients, both in- and outpatients.

#### Learning Objectives:

- Technical innovation enables point of care leucocyte measurement in clozapine therapy.
- Point of care measurement is preferred by patients who have a preference.

**Source of Funding:** Unrestricted grant by Hemocue Sweden

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## **EARLY IMPROVEMENT PREDICTS ENDPOINT RESPONSE TO LURASIDONE IN SCHIZOPHRENIA: POOLED ANALYSIS OF FIVE DOUBLE-BLIND TRIALS**

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Introduction: Early improvement following initiation of treatment is a potentially important predictor of subsequent response that has clinical implications for the successful management of schizophrenia (1, 2). The goal of this pooled completer analysis was to evaluate the clinical value of early improvement in the PANSS total score and the CGI-Severity score as predictors of response to 6 weeks of treatment with lurasidone in patients with an acute exacerbation of schizophrenia. Methods: Data were pooled from 5 similarly designed, six-week, double-blind, placebo-controlled trials of patients hospitalized with an acute exacerbation of schizophrenia who were randomly assigned to fixed, once-daily doses of lurasidone 40-80 mg (n=404) or 120-160 mg (n=264), or placebo (n=280). Endpoint responder rates were calculated using the  $\geq 40\%$  reduction from Baseline in PANSS total score criteria. Early improvement was separately assessed at weeks 1, 2, and 3 using two criteria (CGI-Severity  $\geq 1$ -point improvement; PANSS improvement  $\geq 20\%$ ). Calculations were made of sensitivity and specificity. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-scores for prediction of endpoint response, based on the highest area under the curve (AUC). Results: In the combined lurasidone dose groups, the proportion of subjects showing early improvement was similar for the PANSS  $\geq 20\%$  criterion and the CGI-S  $\geq 1$  criterion, respectively, at week 1 (32.5% and 36.1%) and week 2 (53.8% and 59.8%); but was lower at week 3 for the PANSS  $\geq 20\%$  criterion (70.7% and 88.0%). Endpoint response in the lurasidone group was 50.2% using PANSS 40% responder criteria. For prediction of endpoint response (using the PANSS 40% criterion), PANSS  $\geq 20\%$  improvement at week 1 had 46.6% sensitivity, 81.6% specificity, and AUCROC =0.660. CGI-S improvement  $\geq 1$  at week 1 had 46.2% sensitivity, 74.0% specificity, and AUCROC =0.621. At week 2, PANSS  $\geq 20\%$  improvement had 75.2% sensitivity, 67.8% specificity, and AUCROC =0.733. CGI-S improvement  $\geq 1$  at week 2 had 74.4% sensitivity, 54.8% specificity, and AUCROC =0.650. At week 3, PANSS  $\geq 20\%$  improvement had 91.9%, sensitivity 50.5% specificity, and AUCROC =0.730. At week 3, CGI-S improvement  $\geq 1$  had 87.3% sensitivity, a 43.7% specificity, and AUCROC =0.656. Conclusions: Lack of PANSS improvement at Week 3 was highly predictive of non-response at Week 6. These data are consistent with prior studies with other antipsychotics where lack of early improvement predicted endpoint non-response. Since these results are based on group means, individual response trajectories require further study and should be considered in the clinical decision making and individualization of care in patients with chronic schizophrenia.

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### Learning Objectives:

- At the completion of this session participants will recognize key early improvement variables associated with clinical response in patients with a diagnosis of schizophrenia who are being treated with lurasidone.
- At the completion of this session participants will be able to demonstrate knowledge of how best to individualize the care of patients with chronic schizophrenia.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals Inc.

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### SAFETY AND TOLERABILITY OF CARIPRAZINE IN LONG-TERM TREATMENT OF SCHIZOPHRENIA: INTEGRATED SUMMARY OF SAFETY DATA

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Introduction: Cariprazine, a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors, is in late-stage clinical development for treatment of schizophrenia and bipolar mania. Pooled data from 2 open-label studies evaluated the long-term safety and tolerability of cariprazine in patients with schizophrenia. Methods: This is an integrated summary of safety and tolerability data from two 48-week studies of open-label, flexible-dose cariprazine in adult patients with schizophrenia. In the first study (NCT01104792), new patients and patients who completed double-blind treatment in 1 of 2 lead-in studies (NCT01104766 or NCT01104779) received cariprazine 3-9 mg/day. In the second study (NCT00839852), patients who had completed a separate double-blind lead-in trial (NCT00694707) received cariprazine 1.5-4.5 mg/day. In both studies, a 1-week no-drug screening period was followed by 48 weeks of open-label treatment and a 4-week safety follow-up. Safety evaluations included adverse events (AEs), vital signs, laboratory measures, ECG, ophthalmologic examinations, and assessments on the Barnes Akathisia Rating Scale (BARS) and the Simpson-Angus (SAS). Results: A total of 679 patients were enrolled and received at least 1 dose of open-label treatment with cariprazine; 40.1% completed 48 weeks of open-label treatment with cariprazine. The mean duration of treatment with cariprazine (days  $\pm$  SD) was  $188.4 \pm 136.8$ ; 211 patients (31.1%) were exposed to cariprazine for at least 1 year. In patients entering the extension study, PANSS and CGI-S scores further decreased over the course of the study. Serious AEs (SAEs) were reported in 79 patients (11.6%) including 1 death (suicide) during the open-label treatment period. The most common SAEs were worsening of schizophrenia (4.4%) and psychotic disorder (2.1%). Treatment-emergent AEs (TEAEs) were reported in 553 patients (81.4%). TEAEs reported in at least 10% of patients were akathisia (15.5%), insomnia (13.1%), headache (12.7%), and weight increase (10.5%). Mean change in body weight was small (+2.46 kg). Mean changes in metabolic parameters and other clinical laboratory values, blood pressure, and ECG parameters were generally small from baseline to the end of study. No patients met Hy's law. Mean prolactin levels decreased from baseline to the end of study. The incidence of treatment-emergent parkinsonism (SAS  $>3$ ) was 10.7% and the

incidence of treatment-emergent akathisia (BARS >2) was 17.8%. Ophthalmologic testing revealed no significant changes. Conclusion: Cariprazine administered for up to 48 weeks in adults with schizophrenia was generally safe and well tolerated, with relatively few new AEs compared with acute treatment.

### Learning Objectives:

- At the conclusion of this session, the participant should be able to evaluate the long-term safety and tolerability of cariprazine in the treatment schizophrenia.
- At the conclusion of this session, the participant should be able to understand adverse events associated with long-term cariprazine treatment.

**Source of Funding:** Supported by Forest Laboratories, Inc. and Gedeon Richter Plc

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### **THE EFFECT OF PREVIOUS DOSE OF ORAL ARIPIPRAZOLE (10 OR 30 MG/ DAY) ON THE EFFICACY AND TOLERABILITY OF ARIPIPRAZOLE ONCE-MONTHLY: POST-HOC ANALYSES OF TWO DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS**

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Background: Aripiprazole once-monthly, a long-acting injectable formulation of oral aripiprazole, is the first dopamine partial agonist available as a long-acting injectable formulation. Objectives: To present the efficacy and tolerability of aripiprazole once-monthly in patients stabilized on 10 or 30 mg/day oral aripiprazole before switching to aripiprazole once-monthly 400 mg. Methods: Data from two pivotal double-blind, placebo- or active-controlled trials assessing the efficacy and safety of aripiprazole once-monthly (Kane et al. 2012, 246, NCT 00705783; Fleischhacker et al. 2012, 247, NCT 00706654) were used for this post-hoc analysis. Efficacy was evaluated by change from baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at 4 weeks after initiation of aripiprazole once-monthly. Tolerability was measured as common adverse events ( $\geq 5\%$ ) in this period. Results A total of 841 stable patients (study 246: n=576, study 247: n=265) with schizophrenia were assigned to aripiprazole once-monthly 400 mg. Of these, 105 had been stabilized on 10 mg/day oral aripiprazole (study 246: n=75, study 247: n=30) and 212 on 30 mg/day oral aripiprazole (study 246: n=147, study 247: n=65). In the both studies, aripiprazole once-monthly 400 mg maintained stability of symptoms: 246 study, change in PANSS total from baseline to Week 4: 10 mg group=0, 30 mg group=-0.18; 247 study 10 mg group=-1.03, 30 mg group=-1.83. The most common adverse events ( $\geq 5\%$ ) were injection site pain (range: 9.3% [10 mg/study 246] to 0% [30 mg group/ study 247]); insomnia (range: 9.2% [30 mg/study 247] to 2.7% [10 mg group/ study 246]); weight increase (range 8.2% [30 mg / study 246] to 1.3% [10 mg/ study 246]); agitation (range: 6.2% [30 mg/study 247] to 0% [10 mg group/ study 247]); dizziness (range 5.3% [10 mg/ study 246] to 0% [30 mg/ study 246 and 10 mg/ study 247]); akathisia (range: 7.7% [30 mg / study 247] to 2.7% [10 mg/study 246]); and anxiety (range 6.7% [10 mg /study 247] to 1.5% [30 mg/ study 247]). Conclusion Across two pivotal trials, aripiprazole once-monthly 400 mg maintained stability of symptoms in the month after initiation regardless of whether patients had been stabilized on 10 or 30 mg / day oral aripiprazole. Adverse events occurred at similar rates (none

exceeding 10%) for patients converted from oral aripiprazole 10 or 30 mg / day; and were similar to the entire study population. Overall, for patients stabilized on 10 - 30 mg / day oral aripiprazole, symptoms remain stable for the first 4 weeks after conversion to aripiprazole once-monthly 400 mg.

### **Learning Objectives:**

- Characterize the efficacy of aripiprazole once-monthly for patients stabilized on 10 - 30 mg / day oral aripiprazole.
- To compare the effect of previous dose of oral aripiprazole (10 or 30 mg/ day) on the tolerability of aripiprazole once-monthly.

**Source of Funding:** Supported by Otsuka Pharmaceutical Development & Commercialization, Inc., and H. Lundbeck A/S

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### **PALIPERIDONE PALMITATE DELAYS RELAPSE AND MAINTAINS FUNCTIONING IN PATIENTS WITH STABILIZED PSYCHOTIC AND MOOD SYMPTOMS OF SCHIZOAFFECTIVE DISORDER**

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**Introduction:** Although efficacy of antipsychotics in schizoaffective disorder (SCA) has been reported, few large controlled studies have been performed. Results of the first controlled relapse prevention study of the long-acting injectable antipsychotic, paliperidone palmitate (PP), in patients with SCA are presented. **Method:** This randomized, double-blind (DB), placebo (PBO)-controlled, international study (NCT01193153) included subjects who met SCID-confirmed DSM-IV diagnosis of SCA experiencing an acute exacerbation of psychotic and mood symptoms ( $\geq 16$  on YMRS and/or HAM-D-21). Subjects could continue adjunctive stable doses of antidepressants (AD) or mood stabilizers (MS). After stabilization with PP (78-234 mg), subjects were randomized (1:1) to PP or PBO in the 15-month, DB, relapse prevention period (RPP). Time to relapse was examined using Kaplan–Meier estimates, and between-group comparison was performed using a log-rank test. In addition, Cox proportional hazards regression methodology was used. Patient functioning was examined with the Personal and Social Performance Scale (PSP) as a continuous endpoint using mixed model repeated measures (MMRM) ANCOVA, in addition to categorical evaluations (good functioning, PSP >70; impaired functioning, PSP  $\leq 70$ ) and time to at least 7- and 10-point PSP decrements. **Results:** 667 subjects enrolled; 334 subjects stabilized and randomized (164, PP; 170, PBO) in the RPP. Mean (SD) age: 39.5 (10.7) years; 54% male; 45% monotherapy; 55% adjunctive AD/MS. During the DB period, PP significantly delayed time to relapse ( $P < 0.001$ ). Fifteen percent relapsed in the PP arm and 34% in the placebo arm. Risk of relapse was 2.49-fold higher for placebo (HR 2.49; 95% CI 1.55-3.99;  $P < 0.001$ ) compared with PP. A significant difference (PP vs PBO) favoring PP was observed from DB baseline to 15-month endpoint in PSP (LS mean 3.3; 95% CI 0.68-5.95;  $P = 0.014$ ). The proportion of subjects with good functioning decreased from 50.6% at DB baseline to 41.1% at DB endpoint for placebo; subjects in the PP group maintained good functioning (57.9%, DB baseline; 59.9%, DB endpoint;  $P < 0.001$ ). Time to 7-



and 10-point decrements differed between PP and PBO ( $P<0.01$ ) for both conditions in favor of PP. AEs occurring in  $>5\%$  of patients in any group: weight increased (PP 8.5%, PBO 4.7%), insomnia (4.9%, 7.1%), SCA (3.0%, 5.9%), headache (5.5%, 3.5%), and nasopharyngitis (5.5%, 3.5%). Conclusion: PP as monotherapy or adjunctive to AD/MS significantly delayed relapse in patients with SCA and maintained patient functioning.

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- Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdeken M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res* 2010; 116:107-117.

#### Learning Objectives:

- To determine the role of paliperidone palmitate in delaying time to relapse for patients with schizoaffective disorder.
- To determine the role of paliperidone palmitate in maintaining patient functioning in schizoaffective disorder.

**Source of Funding:** Support: Janssen Scientific Affairs, LLC

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#### **ESZOPICLONE FOR INSOMNIA TREATMENT IN CLINICALLY STABLE PATIENTS WITH SCHIZOPHRENIA: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL**

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Background: Insomnia is a common problem in schizophrenia, yet not well studied. This results in utilization of antipsychotic polypharmacy and excess metabolic side effect burden. Here, we aimed to investigate eszopiclone, a primary insomnia agent, for treatment of schizophrenia related insomnia in an 8-week double-blind placebo-controlled efficacy study, followed by a two-week, single-blind placebo period to evaluate rebound and withdrawal. Methods: In this study, 39 clinically stable patients with schizophrenia or schizoaffective disorder, sleep difficulties at least twice per week in the preceding month, and an Insomnia Severity Index (ISI) score  $> 10$  were randomized to either 3 mg eszopiclone ( $n = 20$ ) or placebo ( $n = 19$ ) for 8 weeks. The primary outcome measure was change in weekly-assessed ISI score. Subjective sleep, core schizophrenia symptoms, depression and quality of life were also assessed. Results: The least square means of ISI decreased more in eszopiclone (mean = -10.7, 95% CI= -13.2; -8.2) than in placebo (mean = -6.9, 95% CI= -9.5; -4.3) with a between-group difference of -3.8 (95% CI= -7.5; -0.2). There were improvements in subjective sleep diary measures in both groups without between-group differences. Depression, schizophrenia, and quality of life measures were similarly not different between groups. Discontinuation rates were similar, and the most common

adverse events were unpleasant taste, sedation, dry mouth and headache. There was no evidence of rebound insomnia and clinical worsening during single-blind period. Conclusion: Eszopiclone stands as a safe and effective alternative for the treatment of insomnia in patients with schizophrenia.

### **Learning Objectives:**

- Treatment of insomnia in schizophrenia.

**Source of Funding:** This project was supported by Sepracor Inc. (now Sunovion Pharmaceuticals Inc.) investigator-initiated project# ESRC131. State of Connecticut Department of Mental Health and Addiction Services supports research at Connecticut Mental Health Center.

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### **VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT: PROGRESS ON THE VALIDATION OF A COMPUTERIZED ASSESSMENT OF FUNCTIONAL SKILLS**

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Background: Assessment of functional capacity is critical to the treatment of cognitive impairments in schizophrenia. Current methods are highly correlated with performance on neuropsychological tests, but suffer from compromised ecological validity due to reliance on role playing exercises. Methods of assessment with improved ecological validity are acutely needed. In response, we have developed a computerized virtual reality assessment that contains the components of a shopping trip, including searching the pantry, making a list, taking the correct bus, shopping, paying for purchases, and getting home. Previous pilot studies indicated that the assessment of functional capacity with virtual reality methodology is feasible, and suggested such a tool may meet criteria for use as a co-primary measure. The primary aims of the current study were to extend our previous results to 1) assess the validity, sensitivity, and reliability of the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) as a primary measure of functional capacity in schizophrenia; 2) examine the VRFCAT's ability to quantify changes in functional capacity by comparing it to the UCSD Performance-based Skills Assessment (UPSA-2-VIM); and 3) determine the association between performance on the VRFCAT and performance on the MATRICS Consensus Cognitive Battery (MCCB), which is the gold standard measure of cognition in pharmaceutical clinical trials regulated by the FDA. Methods: Participants included 100 patients with schizophrenia (60 male, 40 female) and 98 healthy controls (43 male, 55 female). All subjects completed the VRFCAT, UPSA-2-VIM, and the MCCB at Visit 1. The VRFCAT and UPSA-2-VIM were completed again at Visit 2. Key outcome measures for the VRFCAT included total time to complete all objectives as well as errors. Analyses examined test reliability as well as performance differences and correlations between measures. Results: High test-retest reliability was demonstrated for VRFCAT Total Completion Time in both Patient and Control groups (ICCs = 0.90 and 0.75, respectively). Test-retest reliability for the UPSA-2-VIM was also high for both groups (ICCs=.74 and .71 for Patients and Controls, respectively). VRFCAT Total Completion Time was negatively correlated with both UPSA-2-VIM ( $r=-0.55$ ,  $p<0.0001$  for Patients;  $r=-0.56$ ,  $p<0.0001$  for Controls) and MCCB Composite ( $r=-0.47$ ,  $p<0.0001$  for Patients;  $r=-0.60$ ,  $p<0.0001$  for Controls). A factor

analysis will be completed with an increased sample size and will include a newly developed composite score. Conclusions: Findings extend previous results and indicate the VRFCAT is a highly reliable and sensitive measure of functional capacity with associations to the UPSA-2-VIM and MCCB. These results provide encouraging support for a computerized functional capacity assessment for use in schizophrenia.

### **Learning Objectives:**

- Recognize the importance of assessing functional capacity and schizophrenia.
- Understand the potential benefits of computerized assessment using virtual reality methodology.

**Source of Funding:** This work is supported by grant number 1R43MH084240-01A2 and 2R44MH084240-02 from the National Institute of Mental Health.

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### **EFFECT OF LONG-TERM TREATMENT WITH LURASIDONE OR RISPERIDONE ON METABOLIC SYNDROME STATUS IN PATIENTS WITH SCHIZOPHRENIA**

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Background and Objective: Metabolic syndrome is highly prevalent in patients with schizophrenia<sup>1</sup> and is associated with increased cardiovascular morbidity and mortality.<sup>2</sup> The aim of this post hoc analysis was to evaluate the effect of long-term treatment with lurasidone or risperidone on prevalence of metabolic syndrome. Methods: Outpatients with clinically stable schizophrenia were randomized 2:1 to flexibly dosed, once-daily lurasidone (40-120 mg/d) or risperidone (2-6 mg/d) in a 12-month, multiregional, double-blind study that was followed by an open-label extension (flexibly dosed lurasidone 40-120 mg/d for up to 6 months; ClinicalTrials.gov identifier: NCT00641745). NCEP/ATP-III criteria were used to evaluate metabolic syndrome, defined as  $\geq 3$  of the following: waist circumference  $>102$  cm in men or  $>88$  cm in women, triglycerides  $\geq 150$  mg/dL, HDL cholesterol  $<40$  mg/dL in men or  $<50$  mg/dL in women, blood pressure  $\geq 130/85$  mmHg (or antihypertensive medication use), or glucose  $\geq 110$  mg/dL (or antihyperglycemic medication use). Lurasidone and risperidone treatment groups were compared using a chi-square test. Results: The prevalence of metabolic syndrome at baseline of the double-blind phase was similar for the lurasidone (22.8%; 95/416) and risperidone (23.4%; 47/201) groups. After 12 months of treatment, the prevalence of metabolic syndrome (observed cases [OC]) was 20.8% (31/149) with lurasidone and 32.6% (30/92) with risperidone ( $p<0.05$ ). Among patients without metabolic syndrome at baseline, 14.0% (16/114) of lurasidone-treated patients met criteria for metabolic syndrome after 12 months, compared with 21.4% (15/70) of risperidone-treated patients (OC,  $p=NS$ ). Of patients with metabolic syndrome at baseline, 55.9% (19/34) in the lurasidone group no longer met criteria after 12 months, compared with 28.6% (6/21) in the risperidone group (OC,  $p<0.05$ ). For patients taking lurasidone in the double-blind phase who continued on lurasidone in the open-label phase ( $n=109$ ), the prevalence of metabolic syndrome was 20.4% at double-blind baseline and 20.2% after 18 months of treatment. In a similar analysis of patients switched to open-label lurasidone after 12 months of double-blind risperidone treatment ( $n=65$ ), the prevalence of metabolic syndrome was 26.6% at double-blind baseline, 33.8% at open-label baseline (after 12 months of risperidone) and 29.2% after 6 months of open-label lurasidone. Conclusion: Lurasidone

treatment was associated with a lower risk of metabolic syndrome compared with long-term risperidone treatment. The prevalence of metabolic syndrome remained stable over 18 months of continuous treatment with lurasidone, in contrast to increases in prevalence over 12 months of treatment with risperidone. The prevalence of metabolic syndrome decreased in risperidone-treated patients who were switched to lurasidone for 6 months.

#### References:

- Mitchell AJ et al, Schizophr Bull 2013; 39:306-318
- Mottillo S et al, J Am Coll Cardiol 2010; 56:1113-1132

#### Learning Objectives:

- Recognize the importance of evaluating patients with schizophrenia for metabolic syndrome.
- Identify changes in prevalence of metabolic syndrome associated with antipsychotic treatment.

**Source of Funding:** Sponsored by Sunovion Pharmaceuticals Inc.

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#### **ARIPRAZOLE ONCE-MONTHLY FOR LONG-TERM MAINTENANCE TREATMENT OF SCHIZOPHRENIA: A 52-WEEK OPEN-LABEL STUDY**

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Purpose: The primary objective of this 52-week open-label extension study (NCT00731549) was to evaluate the safety and tolerability of aripiprazole once-monthly 400 mg (AOM-400 mg) in the long-term maintenance treatment of schizophrenia. The secondary objective was to evaluate the maintenance of the therapeutic effect. Methods: Patients were new or had participated in 1 of 2 randomized, double-blind, placebo- or active-controlled lead-in studies (246<sup>1</sup> [NCT00705783] or 247<sup>2</sup> [NCT00706654]) assessing the efficacy and safety of AOM-400 mg. The study comprised a screening phase (if applicable), a conversion phase to oral aripiprazole (phase 1, if applicable), an oral stabilization phase (phase 2), and an AOM-400 mg maintenance phase (phase 3). New patients entered at screening and proceeded to phase 1 or 2, depending on their current antipsychotic treatment; patients entering from a lead-in study bypassed screening and phase 1 but were restabilized on oral aripiprazole in phase 2. Only patients meeting stability criteria entered phase 3, in which they received open-label AOM-400 mg every 4 weeks for up to 52 weeks. Study visits were scheduled weekly in phase 1; every second week in phase 2; and in phase 3, weekly for the first 4 weeks, every second week for 8 weeks, and then every 4 weeks through week 52. Results: A total of 1,081 patients entered phase 3: 464 from study 246, 474 from study 247, and 143 new patients; 79.4% (n=858/1081) completed 52 weeks of treatment. The most frequent primary reasons for discontinuation were withdrawal of consent (8.2%), impending relapse (4%: 3.4% with adverse events [AEs] plus 0.6% without AEs), and AEs (2.9%). AEs reported by ≥5% of patients in the extension study were headache (7.6%), nasopharyngitis (7%), anxiety (6.8%), and insomnia (6.6%). The proportion of patients in phase 3 meeting impending relapse criteria (as previously defined [study 246,<sup>1</sup> study 247<sup>2</sup>]) was 8.25% (89/1079). Conclusions: Over 52 weeks, patients participating in an open-label trial of AOM-400 mg had a high completion rate and a low rate of discontinuation due to impending relapse. The

safety and tolerability profile was similar to that observed in the lead-in studies, with no new safety signals. These results suggest that AOM-400 mg maintains effectiveness throughout long-term treatment.

#### References:

- Kane J, Sanchez R, Perry P, Jin N, Johnson B, Forbes, R, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psych* 2012; 73(5):617-624.
- Fleischhacker WW, Sanchez R, Perry PP, Jin N, Peters-Strickland T, Johnson BR, et al. Aripiprazole once-monthly for treatment of schizophrenia: a double-blind, randomised, non-inferiority study.

#### Learning Objectives:

- Understand the safety and tolerability of aripiprazole once-monthly 400 mg in the open-label, long-term maintenance treatment of schizophrenia
- Understand the maintenance of the therapeutic effect of aripiprazole once-monthly 400 mg in the open-label, long-term maintenance treatment of schizophrenia.

**Source of Funding:** Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S

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#### **PSYCHOMETRIC PROPERTIES OF THE DYNAMIC SOCIAL COGNITION BATTERY (DSCB), A COMPREHENSIVE TOOLKIT FOR SOCIAL COGNITION IN PATIENTS WITH SCHIZOPHRENIA**

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Background: Social cognition is a key area of study in schizophrenia and assesses affect perception, social perception, attributional style and theory of mind (ToM). Deficits in social cognition are linked to social dysfunction producing impaired communication and community functioning. The present study analyses the deficits of individuals with schizophrenia in three areas of social cognition using a dynamic image toolkit of tasks of Emotion Processing, ToM and Attributional Style. This study also assesses psychometric properties of a video-based DSCB. Methods: DSCB was administered at baseline and endpoint into a trial assessing cognition in patients with schizophrenia participating in a cognitive intervention study. DSCB consists of i. Emotion Identification, Verbal and Non-verbal Emotion Processing with ratings of 5 basic emotions: happy, surprise, anger, disgust, sad. ii. Dynamic Images ToM videos corresponding with precursors of ToM (emotion recognition), first manifestations (understanding of false belief), and mature aspects (second-order beliefs), iii. Attributional Style: scenarios (positive, negative) through videos. Scale reliability was used to establish internal consistency estimates for the subscale scores. Concurrent validity was assessed by agreement between the DSCB subscales with Facial Emotion Identification task (FEIT). A two-way ANOVA was performance varied across emotions for accuracy rates. Results: Preliminary analysis was performed on 45 patients with schizophrenia. Dynamic images were  $\geq 80\%$  accurate for correct emotion. DSCB has a composite reliability ( $\rho$ ) of  $> 0.80$  with strong internal consistency reliability estimates.

Accuracy scores for emotion states did not differ between dynamic and static faces; however patients were better at identifying and discriminating dynamic than static images. Pearson correlations ( $p < .01$ ) between DSCB Emotion Identification sub-scales (Emotion recognition, Non-verbal Identification, and Verbal Identification) and the FEIT were in the moderate-to-strong range ( $r$ 's = .81, .75 and .59, respectively), as were relations with the tone matching task ( $r$ 's = .78, .71 and .52, respectively). The Emotion Identification, ToM and Attributional Styles demonstrated statistically significant responsiveness to change at 3 months. Conclusions: Overall, DSCB instruments showed good evidence for internal consistency, test-retest reliability, convergent validity, and responsiveness to change over several months. These results support the validity of DSCB to measure social cognition in adults with schizophrenia. Ability to develop new treatments is limited by imprecise measurement tools. Because looking at static images only occurs when looking at photographs, social cognition tasks using dynamic images is more generalizable, and theoretically more linked to the performance on work and social activities. Such knowledge will be effective in the design of novel treatment programs, which could address specific deficits in social cognition.

### **Learning Objectives:**

- The audience will be able to learn the impact of how dynamic and static images are perceived in subjects with schizophrenia.
- The audience will be able to understand the need for a new scale in the assessment of social cognition in subjects with schizophrenia

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## **PREVALENCE, HEALTHCARE UTILIZATION, AND COST OF PATIENTS DUAL DIAGNOSED WITH SCHIZOPHRENIA AND AN ALCOHOL USE DISORDER**

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**Purpose:** Determine the diagnosed prevalence of dual diagnosis with schizophrenia and alcohol use disorder (AUD; defined as alcohol abuse and/or dependence) in a sample of Medicaid patients. Analyze annual healthcare utilization and medical resource costs for patients with a dual diagnosis of schizophrenia and AUD compared to patients with a diagnosis of either schizophrenia or AUD alone. **Methods:** Data from the Truven Health MarketScan Medicaid Multi-State Database were analyzed for the sample of patients with a diagnosis for schizophrenia (DSM-IV: ICD-9 code 195.X), alcohol abuse (DSM-IV: ICD-9 305.X) or alcohol dependence (DSM-IV: ICD-9 303.X) at any time from January 1, 2010 to December 31, 2012. Annual healthcare utilization and costs were compared in patients with a dual diagnosis of schizophrenia and AUD; schizophrenia alone; or AUD alone. Healthcare utilization and cost analyses were conducted in those patients with continuous enrollment from January 1 to December 31, 2012. **Results:** Over the three-year period, 86,118 patients had a diagnosis of schizophrenia, and 18% ( $n=15,787$ ) of those patients had a dual diagnosis of both schizophrenia and AUD. Alcohol abuse (76% of patients) was more common in dual diagnosed patients than alcohol dependence (60%) or both alcohol abuse and dependence combined (36%). For the utilization and cost analyses, the subset of patients with schizophrenia alone ( $n=45,319$ ), AUD alone ( $n=58,240$ ) or a dual diagnosis of schizophrenia and AUD ( $n=10,377$ ) were examined for 2012. A greater percentage of patients with schizophrenia and AUD (75%) visited an ER compared to patients with a diagnosis of either schizophrenia (53%) or AUD (67%) alone. Inpatient admission rates were also higher in dually diagnosed patients (49%) compared to patients with schizophrenia (25%) or

AUD (32%) alone. Dually diagnosed patients had a mean of 1.3 hospitalizations per year, while those with schizophrenia or AUD alone had an average of 0.5 and 0.6 per year, respectively. Dual diagnosed patients also had a greater mean number of total inpatient days per year (8.2) compared to patients with schizophrenia (3.9) or AUD (3.6) alone. Consistent with higher healthcare utilization, dual diagnosed patients had higher annual costs associated with inpatient admissions and ER visits (\$8,497 and \$1,686, respectively) compared to patients diagnosed with schizophrenia (\$3,514 and \$620, respectively) or AUD (\$4,798 and \$771, respectively) alone. Conclusions: These results demonstrate that patients with schizophrenia and AUD have a higher rate of healthcare services utilization, as well as higher annual medical costs compared to patients with a diagnosis of schizophrenia or AUD alone. However, it should be noted that both analyses were conducted only in Medicaid patients using short durations. Therefore, further studies with longer follow up periods are warranted.

### **Learning Objectives:**

- Participants will learn the three-year prevalence of patients dually diagnosed with schizophrenia and AUD.
- Participants will learn the one-year healthcare utilization and corresponding costs of dually diagnosed patients compared to patients with schizophrenia or AUD alone.

**Source of Funding:** Alkermes, Inc.

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## **INSIGHT INTO ILLNESS AND UNCOOPERATIVENESS IN CHRONIC SCHIZOPHRENIA**

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**Objectives:** The objective of this study was to examine factors that might influence insight, uncooperativeness, and self-assessment of quality-of-life using the large National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness CATIE dataset. **Methods:** Insight was assessed by the Insight and Treatment Attitudes Questionnaire (ITAQ) and PANSS item G12 "lack of judgment and insight". Social and occupational functioning was assessed using the Heinrichs-Carpenter Quality of Life (HCQoL) scale, while self-report well-being overall was assessed with the Lehman QoL Interview (LQOLI). Uncooperativeness was assessed by PANSS item G8 ("Uncooperativeness"). **Results:** Consistent with previous reports, we found better insight into illness was associated with higher functioning ( $p<0.05$ ), greater neurocognitive composite ( $p<0.05$ ) and reasoning ( $p<0.05$ ) performance, but there was an inverse correlation to lower self-report well-being overall ( $p<0.05$ ) and a higher level of depressive symptoms ( $p<0.05$ ) in patients with chronic schizophrenia. We also found the inverse relationship at baseline between insight and self-report LQOLI was explained, in part, by levels of depressive symptoms ( $p<0.001$ ) and neurocognitive reasoning impairment ( $p<0.05$ ). Overall cognitive performance was not significant after adjusting for depression effect ( $p>0.05$ ). Among subjects with mild or no depressive symptoms on all 9 items of the Calgary Depression Scale ( $N=839$ ), better self-report well-being overall (LQOLI) was associated with poorer insight ( $p<0.05$ ) and lower cognitive reasoning performance ( $p<0.05$ ) after adjusting for age and symptom severity (CGI-S). Improved insight into illness over time was longitudinally associated

with reductions in uncooperativeness symptoms (PANSS G12) ( $p < 0.001$ ). Conclusions: Our findings suggest that poorer insight and attitudes toward treatment had significant associations with higher level of uncooperativeness, lower level of neurocognitive reasoning, and less depression, which in turn impacts self-report assessment of well-being overall. These results suggest the importance of reducing insight and cognitive impairments both for functional improvement and willingness to accept treatments.

### **Learning Objectives:**

- To understand the impact of insight and treatment attitudes on treatment outcomes.
- To examine factors that might influence insight, uncooperativeness, and self-assessment of quality-of-life in chronic schizophrenia.

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### **SAFETY AND EFFICACY OF ARIPIPRAZOLE LAUROXIL: RESULTS FROM A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY IN SUBJECTS WITH ACUTE EXACERBATION OF SCHIZOPHRENIA**

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*Alkermes, Inc.*

Background: Aripiprazole lauroxil, an extended-release, injectable suspension is being developed as a depot treatment for schizophrenia with an innovative delivery system. Aripiprazole lauroxil is a covalently bonded modification of aripiprazole to form N-lauroyloxymethyl aripiprazole. Conversion of aripiprazole lauroxil to aripiprazole in vivo is governed by slow dissolution from the drug particles followed by hydrolysis, resulting in extended systemic exposure of aripiprazole. Conversion is driven by dissolution of the drug particles and subsequent enzyme-mediated cleavage, generating lauric acid and N-hydroxymethyl aripiprazole. The covalently bonded hydroxymethyl group is then hydrolyzed to aripiprazole. Objective: Evaluate the efficacy, safety and tolerability of once-monthly aripiprazole lauroxil in subjects with schizophrenia (DSM-IV criteria) who were experiencing an acute episode. Methods: Subjects who met eligibility requirements were randomized to one of the following three treatment groups: aripiprazole lauroxil 882 mg IM, aripiprazole lauroxil 441 mg IM, or placebo (Intralipid®) IM for 12 weeks. In addition to IM study drug, based on treatment group assignment subjects received daily oral aripiprazole (15 mg) or matching placebo for the first three weeks after randomization. The primary outcome measure is the change from baseline to Day 85 in the Positive and Negative Syndrome Scale (PANSS) total score. Safety and tolerability were also assessed in all patients who received  $\geq 1$  dose of study drug. Results: Six hundred and twenty-three subjects were randomized across seven countries, including the US ( $n=307$ ), Ukraine ( $n=90$ ), Russia ( $n=73$ ), Bulgaria ( $n=59$ ), Romania ( $n=17$ ), Philippines ( $n=53$ ) and Malaysia ( $n=24$ ). Demographic and baseline characteristics of patients included in the Safety Population ( $n=622$ ) are as follows: 68% male; age (mean $\pm$ SD) 39.7 $\pm$ 11 years; Race: White: 47%, Black or African American: 40%, Asian: 13%; Weight (mean $\pm$ SD): 80 $\pm$ 18.6 kg; BMI: 39% Normal ( $<25$ ); 31% Overweight ( $\geq 25$  to  $<30$ ) and 30% Obese ( $\geq 30$ ); total PANSS score (mean $\pm$ SD): 92.9 $\pm$ 10.7. Approximately 45% of patients have discontinued the study prior to Day 85. Forty-seven patients have discontinued due to an adverse event. Twelve subjects have reported at least one serious adverse event (SAE), including one



death unrelated to treatment (victim of homicide). Conclusions: This study is still ongoing and final analyses have not been completed; however all patients have completed the efficacy assessment phase of the study (Day 85 or early discontinuation). Patient characteristics, retention rate (including the number of patients who discontinued due to an adverse event), and spectrum and incidence of SAEs appear to be comparable to similar studies conducted in this patient population and will be presented in detail. The results of the final efficacy and safety analyses will be presented as well.

### **Learning Objectives:**

- Participants will learn the efficacy of aripiprazole lauroxil for the treatment of schizophrenia.
- Participants will learn the safety and tolerability of aripiprazole lauroxil in patients with schizophrenia.

**Source of Funding:** Alkermes, Inc.

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### **HOW DOES THE NSA-4 COMPARE TO THE NSA-16?**

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**Introduction (Aims).** The 16-item Negative Symptom Assessment (NSA-16) is increasingly used as a validated measure to track response to treatment of negative symptoms in clinical trials of schizophrenia. The NSA-16 takes up to a half hour to administer. Alphas et al. (2011) have proposed a four-item version, the NSA-4, as a reliable and valid brief alternative. The current study is an attempt to replicate the previous findings of Alphas et al. in two randomized clinical trials. **Methods.** Central raters from a well-trained independent and blinded cohort with ongoing monitoring to ensure calibration and prevent drift interviewed subjects in two placebo-controlled randomized double-blind studies of schizophrenia with prominent negative symptoms using live two-way videoconferencing at screen, baseline, and 11 more visits, including end point. At each visit, raters administered the PANSS immediately followed by the NSA-16. **Correlations** between the NSA-16 and the NSA-4 were examined for the NSA global rating, the PANSS negative and positive subscales, and several Marder factors. In addition, Cronbach's alpha and interrater reliability were examined for both scales. **Results.** The NSA-16 was administered 2804 times by 29 central raters to a total of 483 subjects in the two trials. Overall, the correlation between the total scores of the NSA-4 and NSA-16 was very good (0.86). Good convergent validity of the NSA-4 was demonstrated by correlations between the NSA-4 and the NSA global rating, as well as the PANSS negative subscale and the PANSS negative symptoms Marder factor of 0.67, 0.73, and 0.73, respectively. Alphas et al. found these correlations to be 0.68, 0.52, and 0.57. Divergent validity in our sample was demonstrated by low correlations between the NSA-4 and the following PANSS Marder factors: anxiety/depression, disorganized thought, hostility/excitement, and PANSS positive symptoms: -0.11, 0.29, 0.03, and 0.13, respectively. Comparable values in the Alphas et al. study were: -0.03, 0.42, 0.06, and 0.23. Cronbach's alpha, as expected for a shorter scale, was lower for the NSA-4 in our studies as well as the Alphas et al. study. We found it to be 0.65, compared to 0.64 for Alphas et al.; the NSA-16 in our study was 0.87 compared to 0.85 for Alphas et al. Our interrater reliability estimate for the NSA-16 was 0.97, compared to Alphas et al. 0.87. Our ICC for the NSA-4 was 0.94 while Alphas et al. was

0.82, both in the excellent range. Conclusions. The PANSS and NSA-16 in this study were not administered independently of one another, so the usefulness of the NSA-4 alone can only be evaluated in the context of its pairing with the PANSS. Overall, results were very similar to those obtained by Alphs et al. In the hands of highly trained and calibrated central raters, the NSA-4 had very good overall agreement with the NSA-16, and even higher convergent and divergent validity and interrater reliability than was demonstrated by Alphs et al.

#### **Learning Objectives:**

- To discover if previous study results can be replicated.
- To learn how the psychometric properties of the NSA-4 compare to the NSA-16 scale for use in clinical trials.

**Source of Funding:** Funded by Medavante.

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#### **INHALED LOXAPINE AND INTRAMUSCULAR LORAZEPAM IN HEALTHY VOLUNTEERS: A RANDOMIZED, PLACEBO-CONTROLLED DRUG-DRUG INTERACTION STUDY**

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**Objective:** To compare the pharmacodynamic effects and safety of single-dose inhaled loxapine plus intramuscular (IM) lorazepam versus each agent alone (NCT01877642). **Background:** Inhaled loxapine administered via the Staccato® system reduces agitation in patients with schizophrenia (1) or bipolar I disorder (2). Lorazepam is commonly used for agitation and is often administered with other agents; its interaction with inhaled loxapine has not been studied previously. **Methods:** Randomized, double-blind, cross-over study in healthy volunteers. Primary endpoints were maximum effect (minimum value) and area under the curve (AUC) from baseline to 2hr post treatment for respirations/min and pulse oximetry with: concomitant inhaled loxapine 10mg + IM lorazepam 1mg vs. inhaled loxapine 10mg + IM placebo or IM lorazepam 1mg + Staccato® placebo. LS-means [90% CI] for ratios of values for concomitant treatment vs. each drug alone were derived and equivalence confirmed by 90% CI within 0.8-1.25. Subjects were exposed to each treatment in random order, with a 3-day washout between. Blood pressure (BP), heart rate, and sedation (100mm visual analog scale [VAS]) were assessed, and AEs recorded. **RESULTS:** All 18 subjects (mean 20.4 years; 61% male) completed the study. No significant interaction was seen for inhaled loxapine + IM lorazepam on respiration or pulse oximetry vs. each drug alone during 12hr post-dose, with 90% CI for AUC and Cmin ratios confirming equivalence. BP and heart rate were unchanged for 12hr post-dose with inhaled loxapine + IM lorazepam vs. each drug alone. Results clearly demonstrated the central nervous system sedative effects of inhaled loxapine, IM lorazepam, and the combination of inhaled loxapine + IM lorazepam in healthy volunteers. No deaths, serious AEs, premature discontinuations due to AEs, or treatment-related AEs were reported. **Conclusions:** No effects on respiration or vital signs were seen for inhaled loxapine + IM lorazepam vs. each drug alone. There was greater sedation with IM lorazepam + inhaled loxapine compared with either drug administered alone in these healthy volunteers.

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- Kwentus J, Riesenberger RA, Marandi M, Manning RA, Allen MH, Fishman RS, Spyker DA, Kehne JH, Cassella JV: Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. *Bipolar Disord* 2012; 14:31-40.

### **Learning Objectives:**

- Understand the effects on respiration and pulse rate of inhaled loxapine coadministered with IM lorazepam.
- Discuss the safety of two agents used to control acute agitation when administered together and separately.

**Source of Funding:** Study funded by Alexza Pharmaceuticals. Medical writing support, funded by Teva Pharmaceuticals, was provided by Karen Burrows, MPhil, of Excel Scientific Solutions.

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### **VALIDITY CHARACTERISTICS OF THE COGNITIVE ASSESSMENT INTERVIEW (CAI) IN STABLE OUTPATIENTS WITH SCHIZOPHRENIA**

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Introduction: The Cognitive Assessment Interview (CAI) is a 10-item, semi-structured, interview-based measure of cognitive functioning derived from the Clinical Global Impression of Cognition in Schizophrenia (CGI-CogS) and the Schizophrenia Cognition Rating Scale (SCoRS). In validation studies, the CAI scale showed good psychometric properties including excellent reliability, and significant correlations with the MATRICS Consensus Cognitive Battery (MCCB), and functional capacity measures. The objective of these analyses was to further evaluate the CAI in the context of a 29-site, randomized, double-blind, antipsychotic clinical trial in outpatients with schizophrenia. Methods: At baseline, stable schizophrenia patients (n=323) were randomized to receive either Lurasidone or Risperidone, most of whom (n=242) participated in this cognition sub-study. The CAI was administered as an interview-based measure of cognition and objective neurocognitive performance was assessed using the MCCB. Functional capacity was assessed with the University of California San Diego (UCSD) Performance-based Skills Assessment - Brief Version (UPSA-B). Symptom assessment measures included the Positive and Negative Syndrome Scale (PANSS) total score and subscale scores. Pearson correlation of baseline CAI scores with UPSA-B and MCCB were conducted in these analyses. Results: The CAI rater composite score, rated based on direct patient interview and integrating patient and informant information, (N=234) significantly correlated with the MCCB composite score ( $r = -0.27$ ,  $p < 0.001$ ) and with the UPSA-B total score ( $r = -0.30$ ,  $P < 0.001$ ). In the subgroup of patients with an informant (n=86), CAI rater composite score correlated with UPSA ( $r = -0.31$ ,  $P = 0.004$ ), but not MCCB ( $P = 0.18$ ). CAI scores rated from interviewing the patient (N=232) and the informant (N=87) were similar and highly correlated with the CAI rater composite score ( $r = 0.91$  and  $0.96$ , respectively;  $P < 0.001$ ). Both CAI patient and CAI informant scores were correlated with functional capacity (UPSA-B) [ $r = -0.22$ ]

( $P < 0.001$ ) and  $-0.27$  ( $P = 0.01$ ), respectively]. There was no significant difference in the correlations of CAI patient and CAI informant scores with UPSA-B ( $P = 0.51$ ). The magnitude of correlations between CAI patient and CAI informant scores with the MCCB composite score were not significantly different [ $-0.20$  ( $P = 0.002$ ) and  $-0.14$  ( $P = 0.200$ ), respectively;  $P = 0.19$ ]. The 10 CAI items as assessed by the rater correlated significantly with the CAI total score, composite MCCB score, UPSA-B, PANSS negative subscale, but not with the PANSS positive subscale. Conclusions: This cross-sectional analysis of baseline assessment data demonstrates meaningful correlations between the CAI rater composite score and objective cognitive performance (assessed by the MCCB) as well as with a standard measure of functional capacity (UPSA-B). In addition, these correlations were similar whether the CAI was assessed by interviewing the patient, an informant, or using the rater composite. These findings replicate prior data supporting the CAI as a relatively brief, intermediate measure of cognitive functioning suitable for use in both clinical trials and clinical practice.

### Learning Objectives:

- Learn about interview-based measures of cognitive functioning that are suitable for use in clinical trials or practice.
- Learn about methods used for validating interview-based rating scales that assess cognitive functioning

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**Source of Funding:** Sunovion Pharmaceuticals

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### THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS: EFFECTS OF FETAL EXPOSURE ON RISK FOR MAJOR MALFORMATIONS AND EXTRAPYRAMIDAL SYMPTOMS

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Background: Atypical antipsychotics are widely used by reproductive-age women to treat a spectrum of psychiatric illnesses. Despite widespread use of this class of agents 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: Potentially eligible enrollees include pregnant women between 18-45 years old who are capable of providing informed verbal consent. Women are eligible for inclusion if they have used an atypical antipsychotic at any point during pregnancy (exposed); the comparison group is

comprised of women who have not been exposed to these agents. Three phone interviews are conducted: 1) baseline, proximate to the time of enrollment, 2) 7 months gestation, and 3) 2-3 months postpartum. Medical record release authorization is obtained for obstetric, labor and delivery, and the newborn pediatric medical records. Following receipt of medical records, a trained research assistant abstracts relevant information regarding primary and secondary outcomes including: 1) rates of major malformations in infants, 2) birth weight, 3) gestational age at delivery, 4) miscarriage rates, and 5) delivery complications. Data on maternal health outcomes during pregnancy, including weight gain across pregnancy and evidence of gestational hypertension/diabetes, are also obtained. Additional neonatal information regarding extrapyramidal symptoms (EPS) and withdrawal symptoms has been systemically collected from newborn pediatric medical records. Potential major malformations are identified and relevant records are sent to a dysmorphologist blinded to drug exposure for adjudication. A Scientific Advisory Board reviews interim data and determines release criteria for Registry findings. Results: As of February 2014, total enrollment in the Registry was 391 women: 288 women in the exposed group and 103 women in the comparison group. The overall drop-out rate of subjects in the exposed and comparison groups combined was 12%. The proportion of study subjects for whom medical records were obtained was 87%. We previously reported on the risk for major malformations in infants exposed in utero to atypical antipsychotics. This report provides an updated estimate of the relative risk based on larger sample sizes in both the exposed and comparison groups. This report also describes findings regarding the frequency with which a spectrum of extrapyramidal/withdrawal symptoms were observed in both the exposed and comparison groups. Discussion: The NPRAA gathers prospective data regarding risk for critical outcomes following use of atypical antipsychotics during pregnancy. The Registry offers a systematic way to collect reproductive safety information which informs the care of women who use these agents to sustain psychiatric well-being. With increased patient and clinician awareness about the NPRAA, reporting of increasingly reliable risk estimates for outcomes including risk for major malformations in infants is anticipated.

### **Learning Objectives:**

- Provide an updated estimate of the relative risk for major malformations in infants exposed in utero to atypical antipsychotics.
- Describe the estimated frequency with which EPS and withdrawal symptoms are observed in newborns exposed to atypical antipsychotics during the third trimester of pregnancy.

**Source of Funding:** Pfizer (2009-2011), AstraZeneca, Bristol-Myers Squibb, Sunovion, and Ortho-McNeil Janssen.

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### **CRAVING AND DEPRESSION IN OPIATE DEPENDENT MENTALLY ILL RECEIVING SUBOXONE AND GROUP CBT THERAPY**

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Objective: Mental and substance use disorders represent major global public health concerns and are often co-occurring. Studies show craving is an important factor in the development and maintenance of drug use. Moreover, Suboxone has been shown to improve craving and reduce

depression. In this study, we assessed craving and depression in dually diagnosed patients receiving Suboxone and group therapy because most studies evaluated individuals with substance use alone. Methods: Nineteen dually diagnosed African-Americans began the study and thirteen (8 females and 5 males) completed it. Subjects were followed longitudinally, with weekly drug toxicology and treatment intervention (Suboxone and group cognitive behavior therapy-CBT) and quarterly evaluations of craving and depression for 12 months. Results: Average duration of opioid use was 23 years. Craving, frequency and intensity, depression severity, and reported total days of opiate use showed a significant decline from baseline. Craving declined from 8.6 to 5.1 from baseline to month 12. Depression declined from 18.1 at baseline (moderately severe to severe) to 8.3 (mild to moderate) at the 9 month follow-up ( $p < .05$ ). However, depression scores increased slightly at 12 months to 10.8 (moderate). Conclusion: The initiation of Suboxone and CBT resulted in a significant decrease in craving, depression severity, and reported opioid use in opiate dependent mentally ill African Americans.

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**EFFICACY AND SAFETY OF ABT-126, AN  $\alpha 7$  NICOTINIC CHOLINERGIC AGONIST, IN TREATMENT OF COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA: RESULTS FROM A PROOF OF CONCEPT STUDY**

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Abbvie, Inc.*

Background: People with schizophrenia have impaired cognition which compromises functional ability. This study evaluated the efficacy and safety of ABT-126, a potent, highly selective  $\alpha 7$  nicotinic receptor agonist for treatment of cognitive impairment in stable subjects with schizophrenia.

Methods: Design was double-blind, placebo-controlled, parallel-group, multicenter. Eligible subjects receiving stable doses of 1-2 atypical antipsychotics were randomized to ABT-126 10 mg, ABT-126 25 mg, or placebo QD for 12 weeks. The primary analysis was comparison of change from baseline to Week-12 on the MCCB composite score vs. placebo using mixed-model repeated-measures. Other endpoints included UPSA-2, CANTAB battery, and NSA-16.

Results: 207 subjects were randomized and 81% (165/203) completed the study. Mean changes (SE), baseline to Week-12 in MCCB composite were 1.29 (0.95) for 10mg and 1.52 (1.01) for 25 mg ( $p=0.09$ ,  $p=0.07$ , respectively). Greatest improvements were in verbal learning (1.80;  $p=0.06$  for 25 mg), working memory (2.03;  $p=0.05$  for 25 mg), and attention/vigilance (2.65,  $p=0.040$ ; 2.85,  $p=0.04$ ; 10 and 25 mg, respectively). A significant treatment-by-smoking status interaction was observed; whereby nonsmokers (38%) demonstrated treatment differences of 3.1 and 5.2 ( $p=0.02$  and  $<0.001$ , 10 and 25 mg dose groups vs. placebo, respectively). CANTAB results were consistent with MCCB. UPSA-2 and NSA-16 improvements were not significant. The most frequent AEs with ABT-126 were dizziness, diarrhea, and fatigue ( $<8\%$ ).

Conclusions: Overall, ABT-126 demonstrated a procognitive trend. The effect was particularly robust in nonsmoking subjects, with the greatest improvements in verbal learning, working memory, and attention/vigilance. A meaningful effect on negative symptoms was not observed.