



# Wednesday, May 29, 2013

## Poster Session I

### Regency 1 Ballroom

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#### **THE EFFECTS OF BEHAVIORAL PARENT TRAINING AND ACUTE STIMULANT MEDICATION TREATMENT FOR PARENTS WITH ADHD**

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Half of families initiating behavioral parent training (BPT) do not improve. Parental ADHD symptoms may reduce the efficacy of BPT (Chronis et al., 2004), but there are no a priori studies of parents meeting full DSM-IV ADHD criteria. Stimulant medication has been shown to improve parenting (Chronis-Tuscano et al., 2008; Waxmonsky et al., in preparation), but it is not known whether there is additional benefit to receiving medication after completing BPT. This study evaluated the efficacy of BPT for parents with ADHD, and also explored the acute effects of medication on parent child interactions. Participants were 12 parents and their children (ages 6-12) who met DSM ADHD criteria. Parents were first stabilized on stimulant medication during weekly visits with study psychiatrists using the ADHD-RS to titrate to optimal dose. Then, parents discontinued medication and were randomly assigned to a 3, 4, or 5 week baseline, during which they provided semiweekly ratings of their impairment (i.e., Sheehan Disability Scale; SDS; Sheehan et al., 1996), parenting (i.e., Alabama Parenting Questionnaire-9; APQ-9; Elgar et al., 2007) and their child's behavior (i.e., Home Situations Questionnaire; HSQ; Barkley, 1997; Parent Daily Report; PDR; Patterson et al., 1982). After baseline, parents and their children completed two laboratory tasks (Wells et al., 2006), within two weeks, once on their optimally dosed medication and once on a placebo to assess the effects of medication on parent-child behavior. Parents then completed eight BPT sessions, during which they were not medicated. Semiweekly ratings were collected during BPT, and two more parent-child tasks (medication vs. placebo) were conducted upon BPT completion to assess the effects of BPT and the acute effects of medication after receiving BPT.

Data was collected for 12 parents, although two dropped out after the third BPT session. Semiweekly ratings showed that 83.33% of parents reported improved child behavior (i.e., HSQ, PDR), and 50% reported improved parent impairment (i.e., SDS). Only 41.67% of parents reported using less inconsistent discipline, 16.67% reported greater use of positive parenting, and poor monitoring ratings were unchanged.

Observed parent and child behavior was analyzed by 2 (pre-BPT vs. post-BPT) x 2 (medication vs. placebo) ANOVAs. Effects ( $p < .05$ ) of BPT emerged across all parent behaviors (i.e., setting stage, behavior modification, annoy, positive reinforcement, warmth) and some child behaviors (i.e., complain, comply). No medication or interaction effects were found.

BPT, but not medication, was associated with improvements in parent and child behavior. The effects of BPT demonstrated in our study contrast previous studies of parental ADHD and BPT, although previous studies were post hoc between-subject designs, and did not allow for exploration of individual responses to BPT, as in our within-subject study. While we found no medication effects, parents in this study received medication only during the parent-child assessments, and it may be the case that medication effects emerge over a longer period of time, when administered during BPT. These results, although preliminary, suggest that at least some parents with ADHD benefit from BPT.

#### **Learning Objectives:**

- Describe recent research on treatments for parents with ADHD
- Describe the results of a multiple baseline study of examining the efficacy of behavioral parent training for parents with ADHD

- To explore the effects of acute medication treatment for parents before and after receiving behavioral parent training

**Source of Funding:** Not applicable

**Literature References:**

- Chronis-Tuscano et al., (2008). Efficacy of osmotic-release oral system (OROS) methylphenidate for mothers with attention-deficit/hyperactivity disorder (ADHD): preliminary report of effects on ADHD symptoms and parenting. *Journal of Clinical Psychiatry*, 69, 1938-1947.
- Chronis et al. (2004). Enhancements to the behavioral parent training paradigm for families of children with ADHD: review and future directions. *Clinical child and family psychology review.*, 7, 1-27.

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## **DISPOSITION OF D,L-METHYLPHENIDATE IN ORGANIC CATION TRANSPORTER 3 (OCT3) KNOCKOUT MICE**

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**Background:** The organic cation transporter 3 (OCT3, *SLC22A3*), a protein belonging to the solute carrier 22 (*SLC22*) gene family, is extensively expressed in the brain, heart, and some other major organs in both humans and rodents. OCT3 facilitates the transmembrane transport of numerous xenobiotics and endogenous compounds positively charged at physiological pH. A pharmacokinetic (PK) study conducted in *Oct3* knockout (KO) mice has demonstrated that the uptake of the prototypic OCT3 substrate 1-phenyl-4-methyl-pyridinium (MPP<sup>+</sup>) into the heart was markedly lower in the KO mice relative to the wild type (WT) animals (1). Moreover, decreased Oct3 expression in the choroid plexus epithelial cells resulted in significant increase of the concentrations of methamphetamine in several brain regions in mice (2). This study was conducted to determine the effect/role of OCT3 on the disposition of the psychostimulant *d,l*-methylphenidate (*dl*-MPH) in the brain and heart utilizing an *Oct3* KO mouse model.

**Methods:** The study included 2 groups (WT and *Oct3* KO mice). Each group contained 7 males with body weight ranging from 30.0 to 40.0 g. *dl*-MPH was administered via i.p. injection at a dose of 6.0 mg/kg with the injection volume limited to 10 µl/g mouse. The blood, brain, and heart samples were collected 30 min post-administration. The concentrations of *d*- and *l*-isomers of MPH and its primary hydrolytic metabolite ritalinic acid were determined in these samples utilizing an enantiospecific LC-MS/MS assay established in our laboratory (3).

**Results:** The concentrations of *d*-MPH, *l*-MPH, and ritalinic acid in the plasma, brain, and heart were not significantly different between WT and *Oct3* KO mice. However, as has been recognized in human subjects, *d*-MPH concentrations in all tissues tested in both WT and *Oct3* KO mice were significantly higher than *l*-MPH, as a result of stereoselective metabolism of *dl*-MPH by carboxylesterase 1 (CES1).

**Conclusions:** Our study suggests that *dl*-MPH is unlikely to be the substrate of OCT3, and OCT3 does not affect disposition of *dl*-MPH in the brain and heart or otherwise contribute to interindividual PK variability.

**Learning Objectives:**

- The participant will become familiar with the physiological role(s) of the Organic Cation Transporter 3 (OCT3) within the CNS
- The participant will become familiar with the role of OCT3 in the transport of methylphenidate

**Source of Funding:**

This study was supported by NIH grant 1R01DA022475-01A1 (J.S.M.)

**Literature References:**

- 1. Zwart R, et al. Impaired activity of the extraneuronal monoamine transporter system known as uptake-2 in *Orct3/Slc22a3*-deficient mice. *Mol Cell Biol.* 2001;21(13):4188-96.
- 2. Nakayama H, et al. The role of organic cation transporter-3 in methamphetamine disposition and its behavioral response in rats. *Brain Res.* 2007;1184:260-9.

- 3. Zhu HJ, et al. Enantiospecific determination of DL-methylphenidate and DL-ethylphenidate in plasma by liquid chromatography-tandem mass spectrometry: application to human ethanol interactions. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011;879(11-12):783-8.

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### **DOES PHARMACOLOGICAL TREATMENT OF ADHD IN ADULTS ENHANCE PARENTING PERFORMANCE?**

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**Introduction:** Emerging evidence has found that parental ADHD symptoms impair parenting performance (Chronis-Tuscano & Stein, 2012). Most prior research on this topic has relied on self-report; however, there are appreciable limitations of relying on self-ratings of parenting. This study explores the impact of treatment of parental ADHD with lisdexamfetamine dimesylate (LDX) on parenting performance in a laboratory setting.

**Methods:** All adult participants met full DSM IV criteria for ADHD and had a child between the ages of 5-15 with ADHD. There were 44 applicants who were consented of which 38 met all eligibility criteria and elected to participate. Adult participants were optimized on LDX over 3 weeks. In Phase I, parent-child dyads completed two laboratory interactions, once with the adult on blinded optimal dose and once on placebo. The child was unmedicated for both assessments. During each assessment, parents completed age appropriate homework and non-academic tasks (joint play for younger participants and a family problem solving discussion for older subjects) with their child. In Phase II, parents were randomly assigned to continue blinded, optimized treatment or placebo for an additional month followed by a final parent-child interaction task. Parent and child behavior codes were summed to form composite codes based on the Dyadic Parent-Child Interaction Scoring System (Eyberg et al. 2010).

**Results:** Twenty four participants (64%) completed the entire trial. Ten subjects dropped due to adverse events, and four were lost to follow up with most discontinuations occurring during the medication optimization phase. The mean LDX dose was 50mg at the end of the optimization phase. Significant reductions in parental ADHD symptoms were seen with LDX.

Significant reductions in child negative behaviors during the homework task were observed ( $p=.023$ ) in Phase I, but no significant changes in parent behaviors were seen. In Phase II, parents continuously treated with LDX used significantly more praise ( $p=.013$ ;  $ES=1.6$ ), and were more verbally responsive to their child ( $p=.044$ ;  $ES=.48$ ) while reducing their verbalizations ( $p=.043$ ;  $ES=-.58$ ) and commands ( $p=.018$ ;  $ES=-.75$ ). Similar to Phase I, children of parents on active LDX exhibited less negative behaviors ( $p=.028$ ;  $ES=-.71$ ). In addition, parents treated continuously with LDX increased their use of praise over time by threefold ( $p=.003$ ), whereas parents on placebo did not change their rates of praise. Ten subjects (26%) discontinued due to side effects, of which, all were medication naïve at study entry. Loss of appetite, trouble sleeping and headaches were the most common adverse events. There were no serious adverse events or any cases of expressed suicidal ideation or self-harm.

**Conclusion:** Despite the small sample size, treatment of parental ADHD with LDX was associated with improved parenting performance and child behavior in the laboratory setting, with greater effects emerging over time. These results suggest the potential benefits of pharmacologically treating parental ADHD for both parents and their children.

#### **Learning Objectives:**

- to examine the impact of ADHD treatment on parenting behaviors
- to examine the impact of parental ADHD treatment on parent child relationships

**Source of Funding:** This study was funded by an Investigator Initiated grant from Shire Pharmaceuticals to Dr. James Waxmonsky and Dr. Daniel Waschbusch.

## Literature References:

- Chronis-Tuscano A & Stein M (2012). Pharmacotherapy for parents with ADHD: Impact on maternal ADHD and parenting. *CNS drugs* 26(9): 725-732.
- Eyberg, S. M., Nelson, M. M., Duke, M., & Boggs, S. R. (2010). Manual for the Dyadic Parent-Child Interaction Coding System 3.08. from <http://www.pcit.org/>

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## SYMPTOMS OF PERSONALITY DISORDER ARE REDUCED FOLLOWING SUCCESSFUL ADHD TREATMENT

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**Objective:** ADHD frequently occurs within an array of related disorders including a wide range of personality disorders (PD) and traits. Prior studies indicated that high levels of PD symptoms were associated with poor response to treatment for ADHD.<sup>1,2</sup> This reanalysis explored the changes in personality disorder (PD) symptoms and ADHD symptoms, in a clinical trial of OROS methylphenidate (OROS-MPH).<sup>3</sup>

**Method:** 47 adults who met criteria for ADHD were recruited into a double-blind trial followed by an open-label follow up trial with no attempt to include or exclude patients with personality disorder. Symptoms of PD were assessed by the Wisconsin Personality Inventory (WISPI-IV) at baseline (n=47) and at endpoint of the open-label phase (n=27). Symptoms of ADHD were assessed with the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDs).

**Results:** The most elevated PD categories were passive aggressive, obsessive-compulsive, borderline, and avoidant. Z-scores for all PD categories improved significantly from baseline to endpoint ( $p<.05$ ) with effect sizes ranging from 0.4 to 0.9. The two PDs with the highest symptom load at baseline (passive aggressive and obsessive-compulsive) produced effect sizes of  $d=0.9$  and  $d=0.7$  respectively. In comparison, ADHD symptoms improved significantly ( $p<.001$ ) with effect sizes ranging from 2.4 to 3.8. At end-point, average scores for all PDs were at or below the normative mean ( $z\leq 0.0$ ). Change scores for the WISPI-IV and WRAADDs were not significantly correlated.

**Conclusion:** In this clinical trial, we were able to assess personality dimensions and show significant levels of improvement during the clinical trial. At the end of the study, all categories were within normal ranges of the scale. Improvement in personality dimensions was not correlated with improvement in the 3 categories of ADHD symptoms measured by the WRAADDs (emotional dysregulation, attention+disorganization and hyperactivity+impulsivity).

## Learning Objectives:

- Readers will be able to describe changes in symptoms of personality disorder following treatment for ADHD.
- Readers will be able to compare the impact of ADHD treatment on ADHD symptoms versus personality disorder symptoms.

**Source of Funding:** Funding for the primary trial was provided by McNeil Consumer & Specialty Pharmaceuticals; this reanalysis of the data was independently funded.

## Literature References:

- Olsen JL, Reimherr FW, Marchant BK, Wender PH, Robison RJ: The effect of Personality disorder symptoms on response to treatment with methylphenidate transdermal system in adults with attention-deficit/hyperactivity disorder. *Primary Care Companion CNS Disorders*, Published online: October 11, 2012.
- Robison RJ, Reimherr FW, Gail PD, Marchant BK, Williams ED, Soni P, Halls C, Strong RE: Personality Disorders in ADHD Part 2: The effect of symptoms of personality disorder on response to treatment with OROS methylphenidate in adults with ADHD. *Ann Clin Psychiatry*, 2010; 22:94-102.



- Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK: A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry, 2007; 68:93-101.

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## **SAFETY AND FEASIBILITY OF AEROBIC EXERCISE FOR WOMEN VETERANS WITH PTSD**

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**Background:** Conventional treatment strategies for PTSD may be less than optimal in addressing specific needs of women veterans of childbearing age. Research is needed to explore additional therapeutic strategies such as exercise that have potential to improve mental as well as physical health. We piloted an exercise study to determine safety, feasibility and explore efficacy of a structured exercise program in women veterans of childbearing age with symptomatic PTSD

**Method:** Women veterans with symptomatic PTSD completed twelve weeks of moderate intensity exercise. Information on exercise duration, intensity, and side effects was systematically collected. The Clinician Administered PTSD Scale (CAPS) was administered at baseline and at the end of 12-week exercise program. In addition, participants completed weekly assessments of PTSD, depression, and quality of life.

**Results:** Of the fourteen eligible women, six have completed the 12-week exercise program, and four are currently active. There were no major adverse events directly related to exercise and five out six completers no longer met full diagnostic criteria for PTSD (CAPS score of 45 or less) at the end of the study.

**Conclusions:** Our preliminary analyses show that moderate intensity exercise is safe and may offer therapeutic benefit for symptomatic PTSD in women of childbearing potential. Further controlled studies are warranted to determine efficacy of moderate intensity exercise as a treatment modality for this population.

### **Learning Objectives:**

- Summarize treatment advances for PTSD in women
- Integrate exercise, an non-pharmacological intervention for PTSD

### **Source of Funding:**

VISN 17 New Investigator Award

### **Literature References:**

- Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. Cochrane Database Syst Rev. 2008(4):CD004366
- Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence. Washington, DC: Institute of Medicine, 2008

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## **PREFERENTIAL EFFECTS OF METADOXINE ER ON INATTENTIVE SUBTYPE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

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**Objectives:** To examine the effects of metadoxine ER versus placebo on inattentive (IA) versus hyperactive-impulsive (H-I) symptoms and predominantly inattentive (PI) versus combined (CT) subtype in adult Attention-Deficit/Hyperactivity Disorder (ADHD).

**Methods:** This was a 1:1 randomized, double-blind, parallel design study of Metadoxine ER 1,400 mg/day for 6 weeks in 120 adults with ADHD. Efficacy measures baseline to end of treatment were changes in Conners' Adult ADHD Rating Scale (CAARS)-Investigator Rated with prompts IA, H-I, Total

ADHD Symptom scores and TOVA (cpt) ADHD scores and response rates (> 25% or 40% improvement).

**Results:** There was a significant decrease from in CAARS Total ADHD scores in ADHD-PI patients for metadoxine ER (40%) vs. placebo (21%) ( $p < 0.05$ ), while the decrease for patients with ADHD-CT was not significant (27% vs. 26%). Similarly, there was a significant decrease in IA scores in ADHD-PI patients: metadoxine ER (50%) vs. placebo (23%) ( $p < 0.005$ ), while the in ADHD-CT patients was not significant. There was no significant difference in % decreases seen in H-I scores in ADHD-PI or ADHD-CT subjects. Changes in CAARS Total scores were significant for ADHD-PI ( $p < .05$ ), but not for ADHD-CT. Significantly higher response rates at both cut-offs were seen after metadoxine ER vs. placebo in CAARS Total scores were seen in patients with ADHD-PI, but not ADHD-CT. TOVA ADHD Scores were significant decreased after metadoxine vs. placebo for ADHD-PI, but not ADHD-CT.

#### **Learning Objectives:**

- Attendees will learn about the effects of Metadoxine ER on inattentive and hyper-active/impulsive symptoms in adults with ADHD
- Attendees will learn about the effects of Metadoxine ER on predominantly inattentive and combined subtype adult ADHD

**Source of Funding:** Alcobra Ltd.

#### **Literature References:**

- Kessler RC et al. Am Journal of Psychiatry 163:716-723, 2004
- Millstein RB et al. Journal of Attention Disorders 2(3):159-166, 1997
- Kessler RC et al. Arch Gen Psychiatry 67(11):1168-1178, 2010
- Manor I et al. J Clin Psychiatry 73(12): 1517-1523, 2012

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### **DULOXETINE VERSUS PLACEBO IN THE TREATMENT OF PATIENTS WITH GENERALIZED ANXIETY DISORDER WHO WERE 65 YEARS OF AGE AND OLDER**

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**Background:** Generalized anxiety disorder (GAD) is one of the most frequent psychiatric illnesses in the elderly and is associated with significant disability.

**Methods:** Patients with GAD (as defined by DSM-IV-TR), who were at least 65 years of age, were randomly assigned to double-blind treatment with either duloxetine 30 mg to 120 mg/day (N = 151) or placebo (N = 140) for 10 weeks. Dose changes were based on clinical improvement and tolerability; and were implemented in a blinded fashion in 30 mg intervals. The primary efficacy measure was the Hamilton Anxiety Rating Scale (HAMA) total score and the primary endpoint was at Week 10.

Functional impairment was assessed by the Sheehan Disability Scale (SDS) global function score.

Response was defined as  $\geq 50\%$  reduction from baseline in HAMA total score and remission was defined as HAMA total score  $\leq 7$ . Safety and tolerability was assessed by the occurrence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory analyses, and vital signs. Analyses were conducted on an intent-to-treat basis.

**Results:** Most of the patients were female (77.7%), most were white (85.6%), and the average age was 71.6 years (range: 65 to 91 years). At baseline, the mean HAMA total score was 24.5, and SDS global score was 14.0, indicating at least moderate anxiety severity and functional impairment. Completion rates were 75% for placebo and 76% for duloxetine. At Week 10, duloxetine was superior to placebo on mean changes from baseline in HAMA total scores ( $-15.9$  vs.  $-11.7$ ,  $P < .001$ ) and in SDS global scores ( $-8.6$  vs.  $-5.4$ ,  $P < .001$ ). HAMA response rates were significantly greater with duloxetine vs. placebo (71.3% vs. 45.5%,  $P < .001$ ), as were HAMA remission rates (44.8% vs. 29.5%,  $P < .001$ ). Throughout the study,

32% of duloxetine-treated patients remained on 30 mg; 34% were increased to 60 mg; 24% to 90 mg; and 10% to 120 mg. TEAEs that occurred in  $\geq 5\%$  of duloxetine-treated patients and at twice the rate than in placebo-treated patients included constipation (9% vs. 4%), dry mouth (7% vs. 1%), and somnolence (6% vs. 2%). There were three SAEs in the duloxetine group: large intestinal obstruction resulting in death, angina pectoris, and hypertensive crisis. None of the SAEs was considered to be related to receiving duloxetine or due to any protocol procedure. Study limitations included a 10-week treatment period for GAD, which is a chronic disorder; patients with comorbidities common to GAD were excluded.

**Conclusion:** Duloxetine treatment was efficacious in the improvement of illness severity and functioning for patients with GAD who were 65 years of age and older. The adverse event profile for duloxetine was similar to that established for treatment of GAD in the broader adult population.

**Learning Objectives:**

- To evaluate the efficacy, safety, and tolerability of duloxetine 30 mg to 120 mg once daily in the treatment of older patients with GAD.
- To evaluate the efficacy of duloxetine treatment in improving global function.

**Source of Funding:** Eli Lilly and Company

**Literature References:**

- Alwahhabi F. Anxiety symptoms and generalized anxiety disorder in the elderly: a review. *Harv Rev Psychiatry* 2003;11(4):180–193.
- Flint AJ. Generalised anxiety disorder in elderly patients: epidemiology, diagnosis and treatment options. *Drugs Aging* 2005;22(2):101–114.

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**AN OPEN-LABEL PHASE II PILOT STUDY OF THE SAFETY AND EFFICACY OF SELEGILINE TRANSDERMAL SYSTEM (STS) FOR PATIENTS WITH SOCIAL PHOBIA**

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**Introduction:** Controlled clinical trials examining the use of monoamine oxidase inhibitors (MAOIs) for social phobia have shown that MAOIs may be more effective than CBT, placebo, and benzodiazepines in treating symptoms of social phobia. To date, no study has examined the efficacy and safety of selegiline transdermal system (STS) a transdermal MAOI in patients with social phobia. STS has been shown to be an effective and well-tolerated acute and maintenance treatment for major depressive disorder. STS delivers sustained blood levels of monoamine oxidase inhibitor (MAOI) directly into systemic circulation, bypassing first pass metabolism. Dopaminergic effects of STS are of interest with recent evidence that dopamine systems play a role in social phobia.

**Methods:** The objective of this open-label, Phase II, pilot study was to assess the safety and efficacy of selegiline transdermal system (STS) 6 mg/24 hrs in adult patients with clinically defined social phobia. Twenty-one patients were screened, 20 were enrolled and 10 completed this 12 week study. Efficacy was evaluated using the Liebowitz Social Anxiety Scale (LSAS), the Sheehan Disability Scale (SDS), the Clinical Global Impression Severity of Illness Scale (CGI-S) and the Clinical Global Impression Change Scale (CGI-C) for 12 weeks. Safety was evaluated by incidence of adverse events, vital signs and physical examination, clinical laboratory results, and ECG results.

**Results:** Twenty patients were enrolled into open-label treatment with STS 6 mg/24 hrs for 12 weeks. Patient demographics were as follows: mean age of patients was 35 years; 75% were male; and 55% were Hispanic, 40% were Caucasian, and 5% were Black. The results of the primary endpoint analysis showed a statistically significant difference between baseline and end of study in the avoidance component of the LSAS for the ITT population with LOCF ( $p=0.036$ ) and a trend for the anxiety component of the LSAS ( $p=0.053$ ). A statistically significant improvement was also shown from baseline to end of study in symptom severity of illness (CGI-S;  $p=0.023$ ) and change in severity of illness (CGI-C;  $p=0.017$ ). Overall, 75% ( $n=15$ ) of patients reported at least one AE during this study. Three patients (15%) discontinued treatment due to AEs. The most frequently reported AEs by COSTART term were headache



(25%) and application site reaction (20%). All reported AEs were considered either mild or moderate and none were severe. No SAEs were reported during this study.

**Conclusions:** Treatment with STS 6 mg/24 hrs was well-tolerated by patients with social phobia. Patients treated with STS showed improvement compared with baseline scores in multiple efficacy measures. Future double blind trials in larger populations and utilizing a flexible dosing structure appear to be warranted.

**Learning Objectives:**

- Describe the safety of selegiline transdermal system in adult patients with clinically defined social phobia.
- Describe the efficacy of selegiline transdermal system in adult patients with clinically defined social phobia.

**Source of Funding:** This study was funded by Mylan Specialty L.P.

**Literature References:**

- Van Diet IM, den Boer JA, Westenberg, HG. Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine, a selective MAO inhibitor. *Eur Neuropsychopharmacol.* 1992;2:21-29.
- Liebowitz MR, Schneier F, Campeas R, Hollander E, Hatterer J, Fyer A, Gorman J, Papp L, Davies S, Gully R, Klein DF. Phenelzine vs atenolol in social phobia A placebo-controlled comparison. *Arch Gen Psychiatry.* 1992;49:290-300.
- Warwick JM, Carey PD, Cassimjee N, Lochner C, Hemmings S, Moolman-Smook H, Beetge E, Dupont P, Stein DJ. Dopamine transporter binding in social anxiety disorder: the effect of treatment with escitalopram. *Metab Brain Dis.* 2012;27:151-158.
- Moriyama TS, Felicio AC, Chagas MHN, Tardelli VS, Ferraz H, Tumas V, Amaro-Junior E, Andrade L, Crippa J, Bressan KA. Increased dopamine transporter density in Parkinson's disease patients with social anxiety disorder. *J Neurol Sci.* 2011;310:53-57.

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**A RANDOMIZED PLACEBO-CONTROLLED DOUBLE-BLIND TRIAL OF MIRTAZAPINE FOR THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER**

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**Objectives:** Previous open label studies and small trials have suggested that mirtazapine, through its actions on both noradrenergic and serotonergic transmission, it may be effective in improving the symptoms of posttraumatic stress disorder (PTSD) in adults. The aim of this study is to determine the efficacy and tolerability of mirtazapine (Remeron) in the treatment of posttraumatic stress disorder in veterans.

**Methods:** Seventy-eight adult veterans with DSM-IV diagnosis of posttraumatic stress disorder confirmed by the MINI Neuropsychiatric Interview and the Clinician Administered PTSD Scale (CAPS) > 45 were recruited for participation. After signing informed consent and meeting all inclusion/exclusions criteria, subjects were randomized 1:1 to receive either mirtazapine or placebo for 8 weeks. After the 8 week placebo-controlled phase, participants entered an 8 week open-label phase. Mirtazapine was initiated at 15 mg daily at bedtime and increased by 15 mg each week to a maximum of 45 mg daily, as tolerated by the subject (minimum target dose of 30 mg daily). Subjects were assessed at baseline and biweekly by a blinded rater using the Clinician Administered PTSD Scale (CAPS) and Structured Interview for Posttraumatic Stress Disorder (SIP). All randomized subjects who took at least one dose of study medication and had at least one post-baseline efficacy evaluation were included in the intent-to-treat and safety analyses.

**Results:** No significant differences were observed between the mirtazapine and placebo groups based on last observation carried forward. Percent change from baseline to the 8 week endpoint on the SIP total (mirtazapine -19.1 ± 26, placebo -14.7 ± 21) and CAPS total (mirtazapine -19.1 ± 23, placebo -15.9 ± 20)

as well as their subscales, were similar. A significant improvement in Clinical Global Improvement (CGI) score was noted between weeks 2 to 8 for the mirtazapine treated group (n=78, p=0.0164). Mirtazapine and placebo groups were similar in age, length of illness, race, gender, trauma type, and family history. There were no significant differences between the mirtazapine and placebo groups in adverse events or weight gain, although subjects in the mirtazapine group were more likely to endorse sedation/drowsiness (n=8 mirtazapine, n=4 placebo).

**Conclusions/Discussion:** Mirtazapine therapy did not demonstrate efficacy in the treatment of veterans with PTSD in this study. Several factors may explain the lack of efficacy observed with this trial and inconsistency with other reports, including; open label vs. double blind design, non-combat vs. combat related PTSD, duration of PTSD symptoms prior to treatment, and severity of PTSD symptoms based on baseline CAPS scores.

**Learning Objectives:**

- Identify 4 reasons that variable efficacy has been observed in clinical drug trials for PTSD
- State 2 methods for measuring PTSD symptomatology used in clinical drug trials.

**Source of Funding:** Funded through a Merit Grant from the Veteran's Administration Office of Research and Development. NCT 00302107

**Literature References:**

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## **OPRL1 REGULATION OF AMYGDALA-DEPENDENT FEAR IN MICE AND HUMANS WITH PTSD**

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Post-traumatic Stress Disorder (PTSD) is among the most prevalent and debilitating anxiety disorders. Novel pathways and therapeutic approaches for anxiety disorders with altered fear learning, such as PTSD, are needed to improve prevention and treatment. Within the circuitry of fear formation, the amygdala is key, since it is thought to be a critical site of plasticity and storage for fear learning. In the present study we show that expression of a gene (Opioid receptor-like 1, *Oprl1*, encoding the amygdala nociceptin (NOP) receptor) is significantly lowered in a mouse model of dysregulated fear. Systemic or central amygdala infusion of SR-8993, a novel and highly selective NOP receptor agonist firstly used in this study, impairs fear memory consolidation. Furthermore, a human single nucleotide polymorphism (SNP) within *Oprl1* interacts with self-reported childhood trauma to predict PTSD symptoms (n=1793). This SNP also associates with altered fear discrimination (Fear potentiated startle) and altered amygdala-insula functional connectivity (functional magnetic resonance imaging). Together, these data suggest that *Oprl1* is associated with amygdala function, fear processing, and PTSD symptoms. Further, our data suggest that activation of the OPRL1/NOP receptor may interfere with fear memory consolidation, with implications for prevention of PTSD following trauma.

**Learning Objectives:**

- The overall goal was to find concordant genes altered in a PTSD-like mouse model and PTSD patients.
- Test a novel *oprl1* agonist for PTSD prevention in a preclinical study.

**Source of Funding:** All funding obtained by Kerry J. Ressler, MD, PhD. NIH (MH071537, MH096764). Support was received from the NIH/National Center for Research Resources base grant P51RR000165 to Yerkes National Primate Research Center.

**Literature References:**

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## **DETERMINANTS OF POOR SLEEP QUALITY IN INTER-EPISODE BIPOLAR DISORDER**

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**Introduction:** Poor sleep can trigger episodes and be associated with poor outcome in bipolar disorder (BP)(1). Advancing age, high BMI, medical comorbidities, anxiety disorders, smoking, stress, and substance use are associated with poor sleep quality in epidemiologic studies (2). Modifiable variables associated with poor sleep quality can be targeted directly or used as an outcome measure in BP treatment studies.

**Methods:** Euthymic patients with BP (N=156) and healthy controls (HC, N=157) entered the Prechter Longitudinal Study of Bipolar Disorder. The Diagnostic Interview for Genetic Studies, the Hamilton Depression Rating Scale and the Young Mania Rating Scale were administered, height and weight were measured. Questionnaires describing sleep quality (Pittsburgh Sleep Quality Index, PSQI), personality, drug and alcohol use, chronotype, trauma and abuse history, stressful life events, family cohesion, social support and functioning were completed. Multiple linear regression models were constructed to investigate the relationship between PSQI score and independent variables.

**Results:** The average subject with BP was a 41-year old married (42%) or never married (39%), employed female (53%) with a BMI of 29. The average HC was a 33-year old, never married (63%), employed female (47%), with a BMI of 25. BP subjects had poorer sleep quality ( $p=.001$ ), which was positively correlated with number of hypomanic episodes, number of depressive episodes, neuroticism, impulsivity, childhood trauma, and undesirable events in the past 6 months, and negatively correlated with age at onset, family cohesion, social support, and SF36 mental health scale ( $p<.05$ ). PSQI score was higher in those with rapid cycling ( $p=.001$ ) or suicide attempts ( $p=.001$ ), but not alcohol use disorders, drug use disorders, anxiety disorders, psychotic BP or mixed episodes or symptoms. Of medical comorbidities, only self-reported history of cardiovascular disease was correlated with a small increase in PSQI.

A series of multiple linear regressions controlled for age, sex, and BMI were designed to test correlations between sleep quality and significant variables from above as well as clinically important factors. The best fitting model included neuroticism (beta .300,  $p=.002$ ), undesirable events (beta .299,  $p=.003$ ) and mixed episodes (beta .244,  $p=.011$ ).

**Discussion:** Risk factors for poor sleep quality in inter-episode BP included a history of mixed episodes, high neuroticism, and recent stressful life events. As in general population samples, poor sleep quality correlated with neuroticism and stressful life events, which indicates a reactivity to stress during euthymic inter-episodes affecting sleep stability; stress reactivity could be used as a target outcome in treatment studies. Importantly, the subgroup of BP patients with mixed episodes may be a phenotype with higher predisposition to sleep disturbance that should be investigated further with biological measures.

### **Learning Objectives:**

- Poor sleep quality is prevalent even during euthymic inter-episodes in bipolar disorder.
- Mixed episodes and stress reactivity are associated with poor sleep quality during euthymic inter-episodes in bipolar disorder.

**Source of Funding:** Funding from the Heinz C. Prechter Foundation, KL2RR033180, Penn State College of Medicine CTSI/NIH.

### **Literature References:**

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## COGNITIVE EFFECTS OF QUETIAPINE XR IN PATIENTS WITH EUTHYMIC BIPOLAR DISORDER

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**Background:** Bipolar patients experience cognitive impairments including deficits in verbal memory, attention and executive functioning that exist during mood episodes and continue throughout periods of euthymia. Currently, no medications have a marketing approval for cognitive enhancement in bipolar disorder (BD). Quetiapine increases synaptic norepinephrine levels, similar to stimulant medications which are used to treat attentional deficits. Given this mechanism of action, we conducted a double-blind, placebo-controlled trial to examine the cognitive and functional impact of quetiapine XR (QTPX) added to a stable mood stabilizer regimen among euthymic BD I and II patients over 6 weeks.

**Methods:** Emory University and Duke University conducted this study from January 2010 to June 2012. Eligible participants were adults aged 18 to 65 with a diagnosis of BD I or II. Patients had to be on a mood stabilizer regimen with no dose changes 8 weeks prior to baseline. Subjects were entered into a 4 week lead-in phase to ensure mood stability prior to randomization. At the baseline visit, subjects were randomized to receive either QTPX or placebo titrated flexibly up to 400mg daily. Neurocognitive testing occurred at baseline, week 2 and week 6. The tests included: the Continuous Practice Test-Identical Pairs (CPT-IP), the Brief Assessment of Cognition in Affective Disorders (BAC-A), and the Brief UCSD Performance Based Skills Assessment-B (UPSA-B).

**Results:** Twenty-three patients were randomized. The placebo-treated subjects achieved significant improvements from baseline on the CPT-IP, Digit sequencing, Token motor task, symbol coding, BAC-A composite score and UPSA-B. There were no significant improvements between baseline and week 6 scores for any subscale for subjects in the QTPX group. Serum QTP concentration was negatively associated with UPSA-B ( $r = -.57$ ) and symbol coding ( $r = -0.44$ ) mean change scores, and positively associated with Tower of London mean change scores ( $r = 0.44$ ), indicating improved performance on only this task with higher QTP concentration. Serum N-desalkyl-QTP levels were negatively associated with mean change scores on the UPSA-B ( $r = -0.76$ ), verbal memory ( $r = -0.66$ ), verbal fluency ( $r = -0.59$ ) and CPT-IP ( $r = -0.80$ ), and positively associated with changes on the Tower of London ( $r = 0.41$ ) and Token motor task ( $r = 0.91$ ).

**Discussion:** Those receiving QTPX added to their mood stabilizer regimen did not show improvement on the cognitive and functional capacity measures while those receiving placebo did demonstrate improvements. This suggests that QTPX may be interfering with practice effects, and the strong correlations (though mostly non-significant) of the cognitive outcomes with serum concentrations of QTP and N-QTP support this theory. The impairment of practice effects was all the more remarkable given that trial completers actually performed the testing 3 times. Additional research on the effects of antipsychotics on cognition is particularly indicated given the wide use of these agents in the many phases of bipolar disorder and the importance of learning new skills as part of the illness recovery process.

### Learning Objectives:

- To appreciate the effect of Quetiapine XR on cognitive function among euthymic bipolar subjects
- To appreciate the effect of Quetiapine XR on performance-based assessments of functional capacity among euthymic bipolar subjects

**Source of Funding:** This research was conducted with support from the Investigator-Sponsored Study Program of AstraZeneca

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**EFFICACY AND SAFETY OF LOW- AND HIGH-DOSE CARIPRAZINE IN PATIENTS WITH ACUTE MANIC OR MIXED EPISODES ASSOCIATED WITH BIPOLAR I DISORDER**

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**Objective:** Cariprazine (CAR) is an orally active and potent dopamine D<sub>3</sub>/D<sub>2</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors in development for the treatment of schizophrenia and bipolar mania. CAR has demonstrated efficacy in patients with acute mania in Phase II (NCT00488618) and Phase III (NCT01058096) studies. This Phase III trial (NCT01058668) evaluated the efficacy, safety, and tolerability of low- and high-dose CAR in patients with acute mania.

**Methods:** This was a multicenter, double-blind placebo (PBO)-controlled, parallel-group, fixed/flexible-dose study of 6-weeks' duration (up to 7-day washout, 3-week double-blind treatment, 2-week safety follow-up). Patients meeting DSM-IV-TR criteria for bipolar I disorder, acute manic or mixed episode, and Young Mania Rating Scale (YMRS) score  $\geq 20$  were randomized to CAR 3-6 mg/d, CAR 6-12 mg/d, or PBO. Patients were hospitalized during screening and for  $\geq 14$  days of double-blind treatment. Primary and secondary efficacy parameters were change from baseline to Week 3 in YMRS total score and Clinical Global Impressions-Severity (CGI-S), respectively, analyzed using an MMRM approach. Safety evaluations included adverse events (AEs), clinical laboratory values, vital signs, ECGs, and extrapyramidal symptom (EPS) scales.

**Results:** A total of 497 patients were randomized and received study drug (PBO, 161; CAR 3-6 mg/d, 167; CAR 6-12 mg/d, 169); 76%, 77%, and 70% of patients, respectively, completed the study. Change from baseline to Week 3 on the YMRS was significantly greater for both CAR groups compared with PBO (LSMD vs PBO: CAR 3-6 mg/d=-6.1; CAR 6-12 mg/d=-5.9;  $P<.001$  [both]). Both CAR groups were also significantly superior to PBO on the CGI-S (LSMD vs PBO: CAR 3-6 mg/d=-0.6, CAR 6-12 mg/d=-0.6;  $P<.001$  [both]). Significantly more CAR patients met YMRS response ( $P<.001$  [both]) and remission ( $P<.01$  [both]) criteria. The most common ( $\geq 5\%$  and twice the rate of PBO) treatment-related AEs (TEAEs) for cariprazine were akathisia (both CAR groups), and nausea, constipation, and tremor (CAR 6-12 mg/d only). Significantly more CAR 6-12 mg/d patients vs PBO discontinued due to AEs (15% vs 5%); 9% of CAR 3-6 mg/d discontinued. CAR was associated with greater incidence of EPS-related TEAEs than PBO (PBO, 14%; CAR 3-6 mg/d, 36%; CAR 6-12 mg/d, 34%).

**Conclusions:** Results of this study demonstrated that both low- and high-dose CAR was effective in the treatment of acute manic or mixed episodes associated with bipolar I disorder. CAR was generally well tolerated in this group of patients, although the incidence of EPS-related AEs was greater for cariprazine than placebo.

**Learning Objectives:**

- Understand the efficacy of low- and high-dose cariprazine in the treatment of acute mania associated with bipolar I disorder
- Understand the safety and tolerability profile of cariprazine in patients with bipolar I disorder

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

**Literature References:**

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**LURASIDONE MONOTHERAPY FOR THE TREATMENT OF BIPOLAR I DEPRESSION: RESULTS OF THE 6-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY (PREVAIL-2)**

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**Objective:** To evaluate the efficacy and safety of lurasidone, flexibly dosed at 20-60 mg/day or 80-120 mg/day, in the treatment of major depressive episodes in patients with bipolar I disorder without psychotic features.

**Methods:** Subjects (N=505) meeting DSM-IV-TR criteria for bipolar I depression, with or without rapid cycling, with a MADRS score  $\geq 20$  and a Young Mania Rating Scale (YMRS) score  $\leq 12$ , were randomized to 6 weeks of once-daily, double-blind treatment with either lurasidone 20-60 mg, lurasidone 80-120 mg or placebo. Primary and key secondary endpoints were change from baseline to week 6 endpoint in MADRS and CGI-bipolar severity (CGI-BP-S) depression scores, respectively, analyzed using mixed model repeated measures (MMRM).

**Results:** Study completion rates were 74.1% in the lurasidone 20-60 group (mean modal dose, 34.9 mg/d), 73.4% in the lurasidone 80-120 group (mean modal dose, 92.3 mg/d) and 74.7% in the placebo group. Lurasidone treatment resulted in significantly greater reduction in MADRS scores at Week 6 endpoint for both the lurasidone 20-60 group (-15.4;  $p < 0.001$ ; effect size=0.51) and the lurasidone 80-120 group (-15.4;  $p < 0.001$ , effect size=0.51) vs. placebo (-10.7). Lurasidone treatment resulted in significantly greater endpoint reduction in CGI-BP-S depression scores for both the lurasidone 20-60 group (-1.8;  $p < 0.001$ ) and the lurasidone 80-120 group (-1.7;  $p < 0.001$ ) compared with placebo (-1.1). Responder rates (reduction in MADRS  $\geq 50\%$ ) were significantly higher for lurasidone 20-60 (53%) and lurasidone 80-120 (51%) compared with placebo (30%;  $p < 0.001$  for both comparisons). Discontinuation rates due to adverse events for lurasidone 20-60 (7%) and lurasidone 80-120 (6%) were similar to placebo (6%). For lurasidone 20-60, lurasidone 80-120, and placebo, respectively, the most frequently reported adverse events were nausea (10.4%, 17.4%, 7.7%), headache (14.0%, 9.0%, 11.9%), and akathisia (7.9%, 10.8%, 2.4%). Minimal changes in weight, lipids and measures of glycemic control were observed.

**Conclusions:** In this study, monotherapy with lurasidone, flexibly dosed at 20-60 mg/day or 80-120 mg/day, significantly reduced depressive symptoms in patients with bipolar I depression compared to placebo. Tolerability and safety of lurasidone was consistent with results of previous studies.

**Learning Objectives:**

- At the conclusion of the presentation, participants will have a better understanding of the efficacy of lurasidone as a monotherapy treatment of bipolar depression
- At the conclusion of the presentation, participants will have a better understanding of the safety of lurasidone as a monotherapy treatment of bipolar depression

**Source of Funding:** This study was sponsored by Sunovion Pharmaceuticals Inc.

**Literature References:**



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## TREATMENT SERVICE UTILIZATION IN A COMPARATIVENESS EFFECTIVENESS STUDY OF BIPOLAR DISORDER

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**Introduction:** Bipolar Disorder is a severe, chronic mental illness with a high incidence of medical and psychological comorbid conditions. Yet, reports of how patients use medical and psychological services have been mixed. We investigate predictors of service use in the Lithium Treatment - Moderate dose Use Study (LiTMUS). We expect that participants with greater overall severity of illness, mood symptoms, side effects, and lower functioning will use more services. We hypothesize that more psychiatric and medical comorbidities (e.g., high lipid profiles, fasting plasma glucose, obesity) is associated with a higher frequency of services, particularly medical services. Finally, we anticipate that individuals who sought psychological services would tend to be Caucasian and younger.

**Methods:** LiTMUS was a six-month multi-site, randomized effectiveness trial designed to assess the efficacy of flexible, moderate doses of lithium in the context of optimized, personalized pharmacologic treatment (OPT) as compared to OPT alone. Two hundred eighty three currently symptomatic individuals with bipolar disorder were enrolled. Service use was measured with the Cornell Services Index (Sirey et al., 2005) at weeks 12 and 24. Marginal models were fit assuming a natural log link function, a Poisson variance, and a common within-patient association (i.e. exchangeable). Correlation matrices were estimated using generalized estimating equations (GEEs). This model specification yielded estimated incidence rate ratios (IRR) between levels of given predictor variables.

**Results:** Individuals with worse subjective depressive symptoms (IRR=1.02,  $p=0.03$ ) and manic symptoms (IRR=1.04,  $p=0.045$ ) demonstrated higher rates of using medical services. And participants experiencing more intense (IRR=1.11,  $p<0.01$ ) and burdensome (IRR=1.17,  $p<0.01$ ) physical side effects used more overall services. Participants with more psychiatric comorbidities, particularly anxiety and psychotic disorders, had higher rates of using all services (IRR=1.25,  $p<0.01$ ), medical services (IRR=1.11,  $p=0.05$ ), and psychological services (IRR=1.35,  $p<0.01$ ). Patients with higher fasting plasma glucose had over two times the rate of using medical services (IRR=2.22,  $p<0.01$ ) and an almost two times lower rate of using psychological services (IRR=0.54,  $p=0.05$ ) than those with normal or low glucose levels. Patients who were older (i.e., middle-aged) (IRR=1.02,  $p=0.01$ ), had lived in the United States longer (IRR=1.02,  $p=0.01$ ), and were unemployed (IRR=0.54,  $p=0.01$ ) had higher rates of using all services.

**Conclusion:** These data suggest that not all individuals with bipolar disorder seek treatment services at the same rate, but instead specific clinical or demographic features may impact the degree to which one seeks treatment, conveying clinical and public health implications and highlighting the need for specific approaches to correct such discrepancies. Research that could further elucidate the service use disparities demonstrated in this study is warranted.

**Learning Objectives:**

- Recognize the unique medical burden that bipolar disorder presents.
- Summarize what demographic and clinical variables influence service utilization and how they do so.
- Apply these findings to clinical settings.

**Source of Funding:**

National Institute of Mental Health, Contract # NO1MH80001

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**COMPARISON OF CHARACTERISTICS OF PATIENTS WHO CONTINUED VERSUS DISCONTINUED LITHIUM AFTER ONE YEAR OF TREATMENT**

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In a naturalistic A total of 244 patients, who were compliant with lithium for one year, were evaluated in the study. Among those 133 decided to continue treatment and 111 discontinued lithium after discussion with their psychiatrist. The authors used a 13 question survey to compare characteristics of patients and possible reasons for discontinuing.

Two groups were divided and compared, where group A were patients who discontinued treatment versus group B who continued lithium. The five most common reasons for discontinuing treatment were as follows. 76% of patients in Group A compared to 22% in group B were bothered by the indefinite course of medication. Second, 69% of group A versus 28% of group B, were effected by the stigma of taking medication. 57% of group A against 16% of group B no longer felt they needed medication. 50% of patients who discontinued lithium after one year, missed "the high" compared to 21% who continued. The fifth most common reason were 48% of patients who no longer continued were bothered by lithium controlling their moods, against 20% of group B. In all cases the p value was statistically significant in less than 0.001.

This study suggests that even though patients continued treatment for one year, there were factors that made it likely they would further become noncompliant. In view of the fact there are few studies on this issue, and more work is needed. Clinicians should focus on educating and counseling patients with these characteristics to ensure adherence with treatment.

**Learning Objectives:**

- To determine if certain characteristics are common amongst patients who become noncompliant with lithium
- Target strategies to enhance compliance

**Source of Funding:** n/a

**Literature References:**

- Manic Depressive Illness Frederick Goodwin, Kay R. Jamison
- Medication adherence Kay R. Jamison

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**IMPACT OF THE PROPOSED DSM-V DIAGNOSTIC CRITERIA FOR MIXED FEATURES IN BIPOLAR DISORDER ON TREATMENT USING AN ANALYSIS OF ARIPIPRAZOLE CLINICAL DATA**

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**Background:** The *Diagnostic and Statistical Manual of Mental Disorders (DSM)* revision (DSM-V) proposes the addition of a “mixed specifier” to the diagnoses of bipolar mania (BPM) and bipolar depression (BPD) if  $\geq 3$  features from the opposite pole are present.<sup>1</sup> We analyzed the large aripiprazole (ARI) patient database to assess what proportion of patients (pts) categorized under the DSM-IV-TR<sup>2</sup> as having BPM or BPD fulfill the new DSM-V definition of mixed specifier and explored how ARI affects outcomes.

**Methods:** Six 3-week trials of ARI monotherapy for BPM were pooled, as were 2 for BPD. Pts in the BPM studies were treated with ARI, haloperidol (HAL), lithium (LI), or placebo (PLB); in the BPD studies, pts were treated with ARI or PLB. Three combination trials vs PLB were also analyzed: 2 studies of ARI + LI or valproate (VAL) and 1 study of ARI + lamotrigine (LAM).

**Results:** In the monotherapy studies, the prevalence of these mixed patients were 676/2006 (34%) in the BPM studies, and 118/690 (17%) in the BPD studies. Differences in response were seen between pts who did or did not meet the new criteria. In the BPM studies, differences in the Young Mania Rating Scale (YMRS) total score at Week 3 (LOCF) between ARI vs PLB, but not between HAL or LI vs PLB, were significant for those who met the new criteria; significant differences were seen between ARI vs PLB and between HAL vs PLB in those who did not meet the new criteria. Adjusted mean changes from baseline in MADRS total score at Week 3 (LOCF) were not significant, both for those who met and for those who did not meet the DSM-V criteria. In the BPD studies, there were no significant differences in the adjusted mean changes from baseline to Week 3 (LOCF) in the YMRS or in the MADRS total scores for those pts who met the new criteria. For pts who did not meet the new criteria, the difference between ARI and PLB was significant for the MADRS total score but not for the YMRS total score. In the 2 ARI+LI/VAL studies, 108/376 (29%) and 66/326 (20%) of pts, respectively, met the new mixed specifier, and in the ARI+LAM study, it was 99/338 (29%).

**Discussion:** Up to a third of subjects in both the monotherapy and combination studies met the new DSM-V criteria for mixed specifier. Differences in response to treatment in the monotherapy studies were observed between those who did and those who did not meet the new criteria. Similar analyses will be performed for the combination studies.

#### **Learning Objectives:**

- Investigate the prevalence of patients with bipolar disorder that have a mixed features specifier, as per the new DSM-V criteria, in the aripiprazole clinical trial datasets.
- Examine the implications of the proposed DSM-V criteria for mixed episodes in the treatment of patients with bipolar I disorder.

**Source of Funding:** This study was supported by Bristol-Myers Squibb (Princeton, NJ, USA) and Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan).

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#### **LONG-TERM SAFETY AND TOLERABILITY OF OPEN-LABEL CARIPRAZINE IN PATIENTS WITH BIPOLAR I DISORDER**

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**Objective:** Cariprazine, an orally active and potent dopamine D<sub>3</sub>/D<sub>2</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors, has demonstrated efficacy in three 3-week studies in acute mania (NCT00488618, NCT01058096, NCT01058668). This Phase III clinical trial (NCT01058668) evaluated the long-term safety and tolerability of open-label cariprazine in patients with bipolar I disorder.

**Methods:** This was a multinational, multicenter, open-label, flexible-dose study of cariprazine (3-12 mg/d) in patients aged 18-65 years with DMS-IV-TR-defined bipolar I disorder. The study duration was 20 weeks (up to 7 day washout, 16-week open-label treatment, and 3-week safety follow-up). Safety evaluations included adverse events (AEs), clinical laboratory values, vital signs, weight, ECGs, Columbia-Suicide Severity Rating Scale (C-SSRS), ophthalmologic examinations, and extrapyramidal symptom (EPS) scales. Symptom severity was evaluated by YMRS total score change from baseline (LOCF).

**Results:** A total of 402 patients received at least 1 dose of cariprazine (Safety Population). The overall completion rate was 33%; the most frequent reasons for discontinuation were withdrawal of consent (20%), AE (16%), and protocol violation (14%). Mean treatment duration was 57.7 days and mean daily cariprazine dose was 6.2 mg/d. No deaths were reported. Serious AEs (SAEs) occurred in 8% of patients; most SAEs were associated with worsening of mania, depression, or akathisia. The most common AEs leading to discontinuation were akathisia (5%) and depression (2%). Treatment-emergent AEs (TEAEs) occurred in 83% of patients. TEAEs reported in ≥10% of patients were akathisia (33%), headache (17%), constipation (11%), and nausea (10%); overall, EPS-related TEAEs were reported in 46% of patients. C-SSRS-rated suicidal ideation and behavior occurred in 9% and 1% of patients, respectively; TEAEs of suicide ideation and suicide attempt occurred in 4 and 3 patients, respectively. Mean body weight increase was <1 kg; 9% of patients had ≥7% weight gain. Mean changes in laboratory values, vital signs, ECGs, and ophthalmology parameters were generally small. Cariprazine treatment was not associated with an increase in prolactin levels. Mean reduction from baseline in YMRS total score (baseline, 26.1 ± 5.0) was -13.6 ± 8.5 at Week 3 and -15.2 ± 9.2 at Week 16.

**Conclusions:** In this open-label study of patients with bipolar mania, treatment with cariprazine 3-12 mg/d for up to 16 weeks was generally well tolerated but was associated with an increased incidence of EPS-related AEs.

#### **Learning Objectives:**

- Recognize the need for safe and tolerable long-term treatment options for bipolar I disorder
- Understand the long-term safety and tolerability profile of cariprazine in patients with bipolar I disorder

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

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## **TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR TREATMENT RESISTANT BIPOLAR DEPRESSION: A NATURALISTIC CASE SERIES WITH CLINICAL OUTCOMES AND OBSERVATIONS**

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**Background:** Bipolar disorders are frequently associated with pharmacotherapy resistant depression. Acute treatment with antidepressants may be ineffective or worsen the course of bipolar illness. Alternative agents such as atypical antipsychotics can have significant side effects, and ECT is an

undesirable option for many patients. Transcranial magnetic stimulation (TMS) offers a potentially important new alternative. However, little is known regarding its efficacy and safety in bipolar illness or the optimal treatment parameters for such use; efficacy trials of TMS have focused primarily on major depressive disorder. This naturalistic case series of adjunctive TMS in patients with BP II or BP NOS type treatment resistant depression aims to provide initial real-world observations regarding the unique promise and challenges of TMS for bipolar illness.

**Methods:** Prospectively collected clinical data was analyzed for 14 consecutive patients with either BP II (n= 10) or BP NOS (n=4) who were referred to our center for diagnostic evaluation and TMS treatment of complicated, non-psychotic depression. All patients had documented treatment resistance and/or intolerance to multiple treatments in the current episode; 4 had previous trials with ECT that were ineffective. The patients all received adjunctive, high-frequency (10 Hz) TMS over the left dorsolateral prefrontal cortex utilizing the NeuroStar device. Baseline and weekly Quick Inventory of Depressive Symptomatology (QIDS-16 SR) ratings were obtained. Data regarding side effects, emergence of activation symptoms and medication changes were collected at each visit.

**Results:** Nine of 14 (64.3%) patients achieved response (at least 50% reduction on QIDS-16 SR) with an average of 24.6 treatments to first response. Four patients (28.6 %) attained remission (QIDS-16 SR < 6) with an average of 24.8 treatments to reach remission. Nine patients required pharmacological intervention because of bipolar activation symptoms that emerged during the course of treatment; all 5 non-responders were among those who developed activation symptoms. Two of our 4 previous ECT non-responders achieved full remission with TMS. Beyond some signs of activation and transient scalp discomfort or headache, no other treatment-related adverse effects were reported.

**Discussion:** This naturalistic case series provides evidence that TMS may be a promising treatment option for patients with bipolar depression. Our patients were all highly treatment resistant, mostly with ATHF levels 3 or above. Several had been chronically depressed in their current episode despite multiple treatment attempts, including ECT. Overall, TMS was well tolerated; there were no drop-outs. While promising, TMS presents unique challenges in bipolar management, including the need for adequate mood stabilization that does not interfere with motor threshold determination. Additionally, concomitant antidepressant pharmacotherapy appears to predispose towards emergent activation during TMS. Controlled trials are required to evaluate optimal treatment parameters and to determine effective concomitant pharmacotherapies that permit adequate cortical excitability while delivering enhanced outcomes.

#### **Learning Objectives:**

- To evaluate potential effectiveness of TMS for bipolar depression
- To elucidate clinical challenges in the application of TMS for bipolar depression

**Source of Funding:** Chicago TMS Specialists, LLC (self-funded)

#### **Literature References:**

- Gilmer WS, Zarnicki JN. Review of transcranial magnetic stimulation for bipolar illness. *Psychopharm Rev.* 2012;47(4):25-32.
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#### **TRANSLATION, LINGUISTIC VALIDATION AND CULTURAL ADAPTATION OF PATIENT CAREGIVER- AND CLINICIAN-RATED SCALES IN MULTINATIONAL CLINICAL TRIALS**

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This poster aims to identify challenges in the translation, linguistic validation and cultural adaptation of clinical outcomes assessments (COAs), including patient-reported, clinician-reported and observer-reported scales used as outcome and safety measures in clinical trials, as well as scales that may be used for other purposes, such as diagnosis and screening. In global trials it is essential that these rating scales are translated appropriately, ensuring conceptual equivalence between the source version and translations,

as well as maintaining consistency across multiple countries while still allowing for necessary cultural adaptation. Language and cultural considerations are important both in ensuring adequate translation procedures are used, and also in determining the most suitable regions to conduct the clinical trial. The US Food and Drug Administration (FDA) guidelines and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) best practice recommendations have focused on patient-reported outcomes, and a well-defined process has become recognized as industry standard for translating these measures. However, other types of scales are also utilized to support primary and secondary endpoints in clinical trials and also require scrutiny with regards to translation procedures. These include observer/caregiver-reported scales, and clinician-reported scales. Current translation and cultural adaptation procedures for PROs will be reviewed, along with recommendations for application of procedures for observer/caregiver- and clinician-reported outcome measures. The importance of localization will also be reviewed. The same language may be spoken in many countries (for example English, Spanish, French), but the same translation is not necessarily appropriate across countries. The poster will consider why scales should be localized for use in different countries, looking at both linguistic issues and concerns with cultural appropriateness of scale content. Recent years have seen a continuation of the trend for trials to expand globally, particularly within the Asia-Pacific region. Many countries in this region have their own particular challenges for translation of COAs, particularly within a multinational trial, where COAs are typically developed in an English-speaking population and may not allow for conceptual equivalence in translation across countries and languages. India, Japan and Korea are examples of countries where cultural differences may require significant cultural adaptation to COAs, and very different written forms pose particular challenges for cognitive assessments. Challenges identified in recent clinical trials will be examined as examples of potential issues that should be taken into consideration when conducting clinical trials in these regions.

#### **Learning Objectives:**

- Understand the guidelines and recommendations for translation and linguistic validation of different types of COAs
- Identify concerns with trials using multiple countries (and hence multiple languages) and how translation issues can help guide site selection

**Source of Funding:** N/A

#### **Literature References:**

- Gjersing et al (2010). Cross-cultural adaptation of research instruments: language, setting, time and statistical considerations. *BMC Medical Research Methodology*, 10, 13
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## **INVERSE LOCALIZATION AND QUANTIFICATION OF EPILEPTIFORM ELECTRICAL ACTIVITY RECORDED FROM ACUTE TRAUMATIC BRAIN INJURY PATIENTS VIA ELECTROENCEPHALOGRAPHY**

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**Introduction:** Because antiepileptic agents eliminate seizures in only about 35% of post-traumatic epilepsy (PTE) cases, many patients can benefit from surgery for epileptogenic focus removal (1). Nevertheless, it can be particularly difficult to localize epileptic foci in PTE due to the complexity of structural brain changes prompted by TBI, and this difficulty is currently seen as deterrent to surgery. Here we investigate the effects of TBI pathology upon EEG localization accuracy for 12 cases of TBI.

**Purpose:** To introduce and demonstrate the use of a novel framework for the accurate localization of cortical electrical activity recorded from (severe) TBI patients via scalp EEG. This framework can also be used for monitoring the effects of pharmacological agents upon the electrical activity of the brain.

**Methods:** Approval for the study was obtained from the Institutional Review Board of the School of Medicine at UCLA. TBI cases used in this study included 12 subjects, from whom MRI volumes (1 mm<sup>3</sup>



voxel size) were acquired at 3T (Siemens Trio TIM) both acutely and chronically. The MRI protocol consisted of CT scans, MP-RAGE  $T_1$ , FLAIR,  $T_2$  TSE,  $T_2$  GRE, and SWI. Brain segmentation was performed in FreeSurfer, followed by manual correction of labeling errors. A regular grid-based mesh was constructed for the head of each subject based on the MRI segmentation and using 60 electrodes. Tissue types accounted for included healthy-appearing and edematous skin, fat, hard and bone, CSF, healthy-appearing and edematous GM and WM, cerebellum, spinal cord, subcortical structures, epidural hemorrhage, connective tissue, muscle, eyes, cartilage, mucus, nerve, teeth, silicone polyurethane (shunt), and air (sinuses). Existing methodologies were used for forward and inverse calculations (2). To quantify inverse localization accuracy, we employed the localization error (LE) metric.

**Results:** Our localization framework tailored for TBI patients can localize cortical sources in the presence of brain injury with an approximate LE of 0.5-1.5 cm for (relatively) superficial sources, and 1.5-2.0 cm for deep sources (e.g. insula and cingulate cortex). For those sources located within a contusion or pericontusionally, the amount of localization error due to pathology omission is found to be appreciable, which highlights that accounting for pathology is very important for accurate localization.

**Importance:** Despite the potential clinical usefulness of EEG source localization for TBI to investigate the effects of pharmacological agents, few studies explore this topic. Whereas standard source localization techniques can prove inaccurate in the presence of TBI-induced pathology, our contribution features a uniquely accurate framework for EEG source localization in TBI patients. This workflow offers the ability to localize cortical activity using highly realistic anatomical models, thereby providing opportunities to inform patient treatment and affect recovery.

#### **Learning Objectives:**

- To introduce and demonstrate the use of a novel framework for the accurate localization of cortical electrical activity recorded from (severe) TBI patients via scalp EEG.
- To introduce a methodology for monitoring the effects of pharmacological agents upon the electrical activity of the brain.

**Source of Funding:** This work was supported by NIH grants 2U54EB005149 and P01NS058489.

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## **DIFFERENTIAL EFFICACY OF ADJUNCTIVE QUETIAPINE SR IN MIXED STATES OF BIPOLAR DISORDER: FINDINGS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY**

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**Background and Purpose:** Mixed States (MS), intrinsic and severe presentations of BD, constitute >50% of all syndromal episodes in BD with associated treatment refractoriness and elevated risk for suicide. Observational evidence indicates that MS are frequently associated with prominent anxiety and co-morbid substance use disorders.

Despite the common presentation of MS, and associated socio-occupational dysfunction, treatment options, both acutely and long term, are limited. Quetiapine is the only pharmacological agent that has demonstrated efficacy, as monotherapy, in the acute treatment of bipolar mania and depression as well as in prophylactic treatment of BD. To our knowledge, this is the first controlled study to assess the efficacy of quetiapine in the treatment of MS of BD.

Most reports of treatment efficacy in MS are post hoc analysis of clinical trials that included both manic and MS subjects. No study has reported separate outcomes on depressive and manic components of MS in

either acute or prophylactic treatment. This presentation will focus on differential efficacy of adjunctive quetiapine SR on depressive and manic symptoms in MS.

**Methodology:** This prospective 24-week, double-blind, randomized study (n=24) assesses the differential efficacy of quetiapine SR on depressive and manic symptoms of MS when added to ongoing treatment regimen with mood stabilizers, lithium, valproate or lamotrigine. Primary efficacy was assessed by Mixed effects repeat measure of change from baseline in Bipolar Inventory of Signs and Symptoms (BISS) total score and, secondarily, manic and depression subscale scores. Response defined as 50% reduction in YMRS and MADRS and time to intervention or discontinuation for any mood episode were additionally used as efficacy measures.

**Results:** We conducted mixed effects repeat measures analyses including medication group, visit and medication by visit interactions. Mixed effects repeat measure analysis indicated significantly greater improvement in CGI-severity score for adjunctive quetiapine plus mood stabilizer group compared to mood stabilizer plus placebo group ( $F=6.52$ ,  $P=0.01$ ,  $DF=89$ ) as well as for GAF scores ( $F=6.60$ ,  $P=0.01$ ,  $DF=88$ ). MADRS total scores were significantly lower for adjunctive quetiapine plus mood stabilizer group compared to mood stabilizer plus placebo group ( $F=13.93$ ,  $P=0.0003$ ,  $DF=91$ ) as were CGI-depression scores ( $F=8.09$ ,  $P=0.005$ ,  $DF=89$ ). YMRS total scores did not differ between the two groups ( $F=2.67$ ,  $P=0.11$ ,  $DF=92$ ) nor did CGI-mania scores ( $F=1.66$ ,  $P=0.20$ ,  $DF=89$ ).

**Importance:** Treatment with a combination of quetiapine SR and mood stabilizers was superior to treatment with mood stabilizers alone in MS of BD. Quetiapine SR was showed greater efficacy in the reduction of depressive symptomatology than manic symptomatology compared to placebo in MS of BD. To our knowledge, this is the first report of a medication regimen that demonstrated greater efficacy in amelioration of depressive symptomatology without concomitant superior reduction in manic symptomatology compared to placebo in MS of BD. Since psychosocial impairment and risk of suicide in MS are a direct function of intensity of depressive symptoms, findings from this study will have a clinical significance

#### **Learning Objectives:**

- Enumerate the high prevalence and associated impact on outcomes of mixed states in bipolar disorder
- Discuss the differential response of depressive and manic symptoms to adjunctive quetiapine SR in mixed states of bipolar disorder

**Source of Funding:** Astra Zeneca

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<sup>6</sup>Autism Trainers Consortium, J.Olson Consulting Group

**Background:** Clinical trials in autism spectrum disorders (ASD) face critical challenges in ensuring rater competency and diagnostic accuracy. The Autism Diagnostic Interview – Revised (ADI-R)<sup>1</sup> and Autism Diagnostic Observation Schedule (ADOS)<sup>2</sup> have become the gold standard measures for classification of ASD. However, there is little information on rater performance on certification exercises for these measures in global clinical trials.

**Methods:** Raters from 18 countries participated in an ADI-R and ADOS training program for a clinical trial in pediatric ASD. Rater experience, education and previous training documentation were evaluated against stringent criteria. Prequalified raters were categorized into one of the following tiers:

1) Research Reliable - scale author training and certification (n=19 ADI-R; n=17 ADOS); no additional training was required.

2) Experienced - previously administered and/or attended training on the ADI-R/ADOS, (n=21); required to view and accurately rate certification video(s).

3) Inexperienced - not experienced with the measures but met education and population experience requirements to attend 1 of 11 ADI-R/ADOS trainings (n=194).

Training encompassed a 5-day meeting including 2.5 days each of ADI-R and ADOS training provided by research reliable trainers from the Autism Trainers Consortium. Following training at meetings, each “inexperienced” rater watched and scored the certification video. Training on Good Clinical Practices (GCPs) was also provided since not all raters had clinical research experience.

**Results:** Agreement for classification of ASD versus non-spectrum diagnosis of the certification video was 100% for both the ADI-R and ADOS for all “experienced” and “inexperienced” raters. There was little variation in scores between “experienced” and “inexperienced” rater groups. On the ADI-R both groups tended to underscore items: 45 (Conventional/instrumental gestures), 56 (Quality of social overtures), 62 (Interest in children) and 70 (Compulsions/rituals). On the ADOS, both groups tended to over score items A2 (Amount of Social Overtures/ Maintenance of Attention), B6 (Spontaneous Initiation of Joint Attention) and B10 (Amount of Reciprocal and Social Communication) and the “inexperienced” group tended to underscore D1 (Unusual Sensory Interest in Play Materials/Person) whereas the “experienced” raters did not. Overall 240 out of 372 raters (65%) passed the initial certification on the ADI-R and 292 out of 388 raters (75%) passed the initial certification on the ADOS.

**Conclusion:** International clinical trials in ASD face the challenge of accurately diagnosing subjects in a standardized way. The ADI-R and ADOS can be effectively and efficiently used to classify participants as spectrum versus non-spectrum by employing an intensive training program that includes a formal assessment of raters. Scores on certification exercises demonstrate consistency between experienced and newly trained raters with the training videos provided.

#### **Learning Objectives:**

- To explore differences in certification for clinical trials on the ADI-R and ADOS across experience levels.
- To explore item level scoring differences on ASD diagnostic assessments using certification videos.

**Source of Funding:** inVentive Health Clinical

#### **Literature References:**

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<sup>1</sup>Brown University

**Background:** Symptom severity as a moderator of treatment response has been the subject of debate over the past 20 years. Each of the meta- and mega-analyses examining the treatment significance of depression severity used the Hamilton Depression Rating Scale (HAMD), wholly, or in part, to define severity, though the cutoff used to define severe depression varied. There is limited empirical research establishing cutoff scores for bands of severity on the HAMD. The goal of the study is to empirically establish cutoff scores on the HAMD in their allocation of patients to severity groups.

**Methods:** Six hundred twenty-seven outpatients with current major depressive disorder were evaluated with a semi-structured diagnostic interview. Scores on the 17-item HAMD were derived from ratings according to the conversion method described by Endicott and colleagues (1981). The patients were also rated on the Clinical Global Index of Severity (CGI). Receiver operating curves were computed to identify the cutoff that optimally discriminated between patients with mild vs. moderate and moderate vs. severe depression.

**Results:** HAMD scores were significantly lower in patients with mild depression than patients with moderate depression, and patients with moderate depression scored significantly lower than patients with severe depression. The cutoff score on the HAMD that maximized the sum of sensitivity and specificity was 17 for the comparison of mild versus moderate depression and 24 for the comparison of moderate versus severe depression.

**Conclusions:** Based on this large study of psychiatric outpatients with major depressive disorder we recommend the following severity ranges for the HAMD: no depression (0-7); mild depression (8-16); moderate depression (17-23); and severe depression ( $\geq 24$ ).

**Learning Objectives:**

- To become aware that recommended cutoffs for grades of severity on the Hamilton Depression Rating scale have not been previously empirically determined
- To become aware of empirically supported cutoffs for grades of severity on the HAMD

**Source of Funding:** none

**Literature References:**

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**CLINICAL AND OPERATIONAL ASPECTS OF THE COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) AND SHEEHAN SUICIDALITY TRACKING SCALE (S-STTS) IN A PSYCHOMETRIC EVALUATION STUDY**

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**Background:** An accurate and objective method to prospectively assess suicidal ideation and behavior is an important priority for clinical CNS drug trials. Even though the FDA has endorsed the Columbia Suicide Severity Rating Scales (C-SSRS) (1) as the “gold standard” in such trials, there have been no published studies comparing operational & other aspects of the C-SSRS (2) with other currently used alternatives such as the Sheehan Suicide Tracking Scale (S-STTS) (3). For this study, we examined various operational aspects of each assessment instrument, including time for interview completion, patient and rater preferences, and the overall ease of use of these assessments.

**Method:** All adult patients admitted to an urban, university-affiliated psychiatric hospital between January 2012 and November 2012 were asked if they were interested in participating in a research study.

A total of 200 adult in-patients participated in this psychometric evaluation study. The mean age of participants was 38.6 ( $SD=12.4$ ). Study design and methodology included stratifying patients by age and psychosis on a 1:1 randomization ratio to vary S-STS administration format (self-report versus interview). Counter-balancing procedures controlled for order sequence of the assessments. The C-SSRS was administered in interview format only. Both patients and interviewers completed an acceptance questionnaire regarding their overall satisfaction and impression of these suicide assessment interviews (4).

**Results:** The average time length for the C-SSRS was 17.8 minutes ( $N = 199$ ,  $SD: 8.7$ ) and 16.18 minutes ( $N = 199$ ,  $SD: 7.4$ ) for the S-STS (interview and self-report). A paired-samples  $t$ -test revealed a statistically significant difference between the C-SSRS and the S-STS on time length,  $t(196) = 3.52$ ,  $p = .001$ . Patient satisfaction ratings on the C-SSRS were compared to satisfaction ratings on the S-STS using within-subjects  $t$ -tests. Satisfaction ratings were slightly higher for the C-SSRS ( $M = 91.5$ ) than the S-STS ( $M = 89.9$ ) as indicated by a marginally significant  $t$ -test,  $t(90) = 1.92$ ,  $p = .059$ . The average global satisfaction score for was highest for the C-SSRS at 90.6 ( $N = 21$ ,  $SD = 10.4$ , Range: 65-100), followed the S-STS at 80.0 ( $N = 10$ ,  $SD = 12.7$ , Range: 50-90). Findings revealed a weaker trend in preference between the C-SSRS to the S-STS  $t(9) = 1.41$ ,  $p = .193$ .

**Conclusion:** Findings indicated the C-SSRS took the longest to administer. The self-report S-STS was more time efficient than an interview format. Second, in regards to global satisfaction, patients had higher satisfaction ratings for the C-SSRS when compared to the S-STS. Finally, regarding the raters' perspective and ease of use a weaker trend was observed in preference between the C-SSRS and S-STS. These results provide an independent evaluation on these assessments and contribute to the existing developer-based research literature for these assessments. In addition, our analysis reveals a unique contribution to the clinical and research literature by incorporating patient and rater preferences.

#### **Learning Objectives:**

- Describe time administration, preferences and efficiency of use for standardized suicide rating scales in clinical-research settings
- Present an independent comparison on findings related to procedural aspects between C-SSRS and S-STS

**Source of Funding:** This study was supported by an investigator initiated award from Pfizer, Inc. to Penn State Hershey Medical Center (Alan Gelenberg, MD PI)

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#### **USE OF A COMMUNITY SAMPLE TO EXPLORE EXTERNAL VALIDITY IN A RANDOMIZED CLINICAL TRIAL**

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**Background:** While randomized clinical trials (RCTs) are generally accepted as reliable for determining treatment effects, practitioners often express concerns about their potential lack of external validity.<sup>1</sup> The frequent gap between RCT populations and “real world” patients with a more complicated clinical presentation is a common criticism. A recent RCT designed to assess the efficacy of atomoxetine in treating attention-deficit/hyperactivity disorder (ADHD) in young (18-30 years old) adults<sup>2</sup> included a community sample (CS) to address this issue.

**Objectives:** The primary objective of the CS analysis was to compare the clinical course of ADHD in clinically complex and clinically simpler (“trial-like”) patients under real world conditions.

**Methodology:** The CS was obtained through the novel web-based process used to recruit RCT study subjects, preparatory to initial site-based evaluations. Respondents screening positive for the likelihood of meeting ADHD criteria (ASRS) and meeting web-based inclusion/exclusion criteria for RCT participation but either declining to participate in the RCT, or expressing a willingness to participate but unable to do so because no site was available in their geographic region, comprised the “trial-like” CS group. Respondents failing to meet web-based inclusion/exclusion criteria formed the “complex” subject group. Clinical data were collected from CS study participants exclusively through web-based surveys on the same reporting schedule as RCT participants. Primary statistical analysis compared complex and trial-like patients on ADHD severity (using CAARS-S:SV total ADHD symptom score) over a 12-week period using mixed model repeated measures with visit #, baseline CAARS-S:SV rating and subject group (trial-like or complex) as independent variables.

**Results:** A total of 962 young adults (18-30 years old) were included in the CS analysis with over two-thirds (669) comprising the complex cohort. The least square mean difference in the CAARS-S:SV total ADHD Symptom score improved (declined) from baseline to 12 weeks after baseline by 0.76 rating-points more among the complex than trial-like patient groups ( $p=.320$ ). This difference was statistically and clinically non-significant.

**Conclusion:** It is operationally feasible to track the progress of a cohort of patients failing to meet protocol criteria during a successfully executed RCT. Initial analysis suggests that the clinical course of trial-like and complex patients after 12 weeks, as measured by differences in the baseline-to-endpoint change in CAARS-S:SV, appears comparable. Further examination of clinical characteristics within the complex population is warranted.

#### **Learning Objectives:**

- Practitioners often express concern regarding the external validity of randomized controlled trials in the evaluation of treatment efficacy.
- The course of ADHD in real world/complex patients appears comparable to that from simpler trial-like patients.

**Source of Funding:** Eli Lilly and Company, Employer

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#### **WHAT PANSS ITEMS DO SITE RATERS HAVE THE MOST TROUBLE RATING?**

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**Background:** The Positive and Negative Syndrome Scale (PANSS) is a complex 30 item instrument for evaluation of multiple domains of psychopathology in schizophrenia (1). In order to inform future training, we ranked the 30 PANSS items with respect to the degree of dissonance in scoring between site raters and same- language local experts utilizing data from ten global schizophrenia trials.



**Method:** Prior to study initiation, raters were trained at investigators meetings by highly interactive procedures, including slide presentations, rating of videotaped patient interviews, and - in some cases interview and rating of live actors trained to portray schizophrenia symptoms. Site PANSS interviews were recorded and uploaded for evaluation by an independent same-language local expert. The external reviewers provided feedback on an ongoing basis to the site and sponsor on diagnostic and scoring accuracy and interview quality (2). The current results are based on data from ongoing and recently completed studies. Additional data will be reported in the future. The number of site rater vs. external rater comparisons in the current analysis ranged from n= 2217 to n =2533 for the 30 PANSS items, respectively.

**Results:** The five PANSS items with the *highest percentage of significant mismatches* (2 anchor points or greater) between the site and external raters were : G13 Disturbance of volition (14.88%), N6 Lack of spontaneity and flow of conversation (13.57%), G15 Preoccupation (13.34%), N7 Stereotyped thinking (12.46%), and P2 Conceptual disorganization (11.83%).

The five items with the *highest percentage of exact matches* were G14 Poor impulse control (69.71%), P7 Hostility (69.32%) G3 Guilt feelings (67.45%), P3 Hallucinatory behavior (66.38%) and G8 Uncooperativeness (64.73%).

**Discussion:** The five PANSS items with the highest *discordance* are scored entirely based on objective observations of behavior and/or speech patterns during the interview. In contrast, the scoring of the items with the highest *concordance* all include data acquired by verbal report from the patient or informant. The results are consistent with the notion that, in the field, inter-rater reliability may be harder to achieve on PANSS items that rely purely on objective observation. If so, inter-rater reliability on such items might be enhanced by focused training. These results are preliminary and additional data is under collection.

**Learning Objectives:**

- The observer will understand which PANSS items are most prone to error by site raters in the field
- The observer will recognize that different PANSS items may require different types of training to achieve precision of measurement

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

**Literature References:**

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**COMPARATIVE VALIDATION OF THE ISST-PLUS, THE S-STs, AND THE C-SSRS FOR ASSESSING SUICIDAL THINKING AND BEHAVIOR**

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**Introduction:** The C-SSRS is FDA-designated as the standard for assessment of suicidal ideation and behavior (SIAB). The ISST-Plus and S-STs have demonstrated validity as alternative scales for collecting related SIAB information.

If the latter scales are used in trials for US regulatory submissions, it is important that they be mappable to FDA-mandated categories. This study examines concurrent validity for mapping these 3 scales to the FDA categories proposed in September 2010 and August 2012.

**Methods:** Experienced raters from an academic clinical setting were formally trained in ISST-Plus, S-STS, and C-SSRS use. Subjects with SIAB of varying levels of severity (“not at all suicidal” to “extremely suicidal”) were sampled from inpatient and outpatient settings and consented to receive 3 separate SIAB interviews by independent raters. The interview sequence for the 3 scales was randomly ordered. Subjects were videotaped if separate consent was obtained. At each interview’s conclusion, the appropriate scale was mapped to categories outlined in the FDA draft guidance documents. Symptom mapping consistency of the 3 scales (and the clinician rated, the patient rated and the reconciliation versions of the S-STS) to the FDA-mandated SIAB categories is reported.

**Results:** 5 raters completed interviews of 45 subjects. Consistency of ratings for each category was identified on the ISST-Plus, S-STS, and C-SSRS. 9 categories were mapped: 1) completed suicide; 2) suicide attempt; aborted attempt; interrupted attempt; 3) preparatory acts toward imminent suicide behavior; 4) overall suicidal ideation; ideation: passive; ideation: active (nonspecific—no method, intent, or plan); ideation: active (method, but no intent or plan); ideation: active (method, intent, but no plan); ideation: active (method, intent, and plan); 5) self-injurious behavior, intent unknown; 6) not enough information (fatal); 7) self-injurious behavior, no suicide intent; 8) other (accidental, psychiatric, medical), no deliberate self-harm; 9) not enough information (nonfatal).

**Conclusion:** The ISST-Plus, S-STS, and C-SSRS represent potentially valuable instruments to identify and categorize SIAB. Differences in categorization observed for the 3 scales may be related to variability in patient reports across interviews, rater reliability, and differences among the scales (eg, interview structure, word choice). Additional psychometric work, including interrater and intrarater reliability, is necessary to support these scales’ validation. These findings increase the range of assessment instrument choices available for the assessment and tracking of suicidality in clinical research. This is the first time all 3 major suicidality assessment scales in all their formats have been validated against each other and all mapped to the classification algorithms and categories proposed in the FDA Draft Guidance Documents on Suicidality Assessment of 2010 and 2012.

#### **Learning Objectives:**

- Be better able to assess suicidality in clinical settings in ways that will protect their patients and improve medico-legal protection
- Be familiar with the psychometric properties of the 3 suicidality rating scales used in research studies and in clinical practice with their strengths and limitations

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

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### **A PROSPECTIVE TRIAL OF CUSTOMIZED ADHERENCE ENHANCEMENT PLUS LONG-ACTING INJECTABLE ANTIPSYCHOTIC MEDICATION IN HOMELESS OR RECENTLY HOMELESS INDIVIDUALS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER**

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**Background:** Treatment non-adherence in people with schizophrenia is associated with relapse and homelessness. Building upon the usefulness of long-acting medication, and our work in psychosocial

interventions to enhance adherence, we conducted a prospective uncontrolled trial of customized adherence enhancement (CAE) plus long-acting injectable antipsychotic (LAI; i.e. Haloperidol decanoate) in 30 homeless / recently homeless individuals with schizophrenia / schizoaffective disorder.

**Methods:** Participants received monthly CAE and LAI (CAE-L) for 6 months. Primary outcomes were adherence and housing status. Secondary outcomes included psychiatric symptoms, functioning, side effects, and hospitalizations.

**Results:** Mean age of participants was 41.8 years (SD 8.6), mainly minorities (90% African-American), mainly single/never married (70%) and with little education (did not finish high school). Most (97%) had a history of past / current substance abuse, and been to jail / prison (97%). Ten individuals (33%) terminated the study prematurely. CAE-L was associated with good adherence to LAI (76% at 6 months) and dramatic improvement in oral medication adherence, which changed from missing 46% of medication at study enrollment to missing only 10% at study end. Mean time in sub-optimal housing went from 56% in the 6 months prior to study enrollment, to 41 % in the first 3 months and 14% in the last 3 months of the study, respectively ( $p=.001$ ). There were significant improvements in psychiatric symptoms and functioning. The major side effect with LAI was akathisia, leading to LAI discontinuation in one individual.

**Conclusion:** While interpretation of findings must be tempered by the methodological limitations, CAE-L appears to be associated with improved adherence, symptoms, and functioning in homeless / recently homeless individuals with schizophrenia/schizoaffective disorder. Proportion of time in sub-optimal housing was decreased. There is a need for additional research on effective and practical approaches to improving health outcomes for homeless people with schizophrenia.

**Learning Objectives:**

- CAE-L appears to be associated with improved adherence, symptoms, and functioning in homeless / recently homeless individuals with schizophrenia/schizoaffective disorder.
- Proportion of time in sub-optimal housing was decreased.

**Source of Funding:**

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## INTENSIVE RATER TRAINING TO STANDARDIZE COGNITIVE ASSESSMENT IN A MULTI-CENTER PARKINSON'S DISEASE TRIAL

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**Background:** The impact of inter-rater reliability on statistical power is well-known to clinical trialists, though approaches to maximizing reliability are variable and often dependent on scale complexity, rater experience, and trial resources. In Parkinson's disease (PD) trials, where cognition as endpoint is in its relative infancy and experienced raters are rare, formal rater training under strict criteria is critical to increase the chance of success.

**Method:** This randomized, placebo-controlled trial examines the effect of rasagiline on cognition in patients with mild cognitive impairment associated with PD. Study endpoints include two well-validated cognitive scales: the Montreal Cognitive Assessment (MoCA; 11 items) and the Scales for Outcomes of Parkinson's Disease – Cognition (SCOPA-COG; 10 items). In effort to maximize rater reliability, a robust training program was deployed prior to study start. Raters completed the following steps prior to administering the scales to study patients: 1) On-line didactic and video training, 2) Post assessment requiring 100% performance, 3) Investigator Meeting scoring practice; and 4) Videotaped administration to a mock patient. Calibrated expert raters reviewed videos and provided feedback to raters. Errors that clearly affected an item score were labeled "major" and required resubmission of a second video. Other administration errors were considered "minor" but were relayed back to raters in the interest of standardization.

**Results:** At the time of submission, a total of 45 raters had started the training program and 24 had completed. While 27% of raters entering the program were classified as inexperienced (defined as 10 or fewer pre-trial administrations) on the MoCA, 81% were inexperienced on the SCOPA-COG. Despite this, there was no significant difference between the MoCA and SCOPA-COG online assessment accuracy, (MoCA 89.7%  $\pm$  12.00; SCOPA-COG 92.2%  $\pm$  15.26;  $p = 0.22$ ) nor on mock scale administration errors (MoCA 4.58  $\pm$  2.78; SCOPA-COG 5.38  $\pm$  2.93;  $p = 0.29$ ). Experienced and inexperienced raters did not differ significantly on administration errors (MoCA: Exp 4.46  $\pm$  2.79, Inexp 5.13  $\pm$  3.31,  $p = 0.74$ ; SCOPA-COG: Exp 7.00  $\pm$  2.55, Inexp 4.75  $\pm$  2.70,  $p = 0.31$ ). The number of pre-

trial scale administrations did not predict training performance, nor did number of formal trainings received or years of clinical experience. Of the 24 raters who submitted administration videos, 14 (58%) required submission of a second video due to major findings. On second submission, only one rater (7%) required further remediation.

**Conclusion:** Despite the relative brevity of the SCOPA-COG and MoCA compared to other measures employed in clinical trials (e.g., MCCB), there is potential for considerable error on these scales. These results support the value of enhanced interventions designed to maximize reliability, regardless of pre-trial clinical or direct scale experience. A multi-step, multi-modal training program such as the one described herein can standardize raters to fidelity with scale instructions, thereby minimizing error variance and increasing study power.

**Learning Objectives:**

- To better appreciate the need for rater standardization on cognitive measures in multi-site trials.
- To understand the value of rater training over experience in scale performance.

**Source of Funding:** Teva Pharmaceuticals

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## **USE OF 'DUAL' RATINGS CRITERIA TO IMPROVE SUBJECT SELECTION AND TRIAL OUTCOMES**

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We compared the “dual” scores from the Inventory of Depressive Symptoms (IDSc30) obtained by site-based clinician raters and centralized (site-independent) raters conducted during a double-blind, placebo-controlled study of patients with acute Major Depressive Disorder (trial CBM-IT-01; BCI NCT 007005003). At the baseline visit, centralized raters scored the total IDSc30 significantly lower than site-based raters ( $p=0.027$ ). In a post-hoc analysis, we examined whether a “dual” scoring concordance range applied as part of the randomization criteria could affect the treatment outcome. Using a criterion of  $\geq$  one standard deviation from the mean baseline IDSc30 as a cut-off, we selected a concordance range of  $\leq 9$  points scoring difference between site-based and centralized raters to exclude the most markedly discordant subjects from the analysis. This criterion identified 85 of the 114 subjects at week 6 (end of treatment) who had concordant “dual” baseline IDSc30 scores.

The “dual” scoring concordance criteria improved the study outcome as assessed by both treatment response and remission criteria. Relative to the unfiltered, total group of 114 subjects at week 6, the placebo response rates dropped by over 3 points from 32.3% to 29.2% and the drug effect between the candidate drug combination and placebo increased from 15.9% to 19.4%. Similarly, the drug effect based upon remission rates improved from 4.7% to 9.0%. These data suggest that external review used to confirm symptom severity and affirm appropriate subject selection prior to randomization may improve study outcomes.

**Learning Objectives:**

- To explore the utility of external review to improve ratings precision
- To determine with “dual” concordance ranges can affect trial outcomes

**Source of Funding:** BrainCells Inc (San Diego, California) CBM-IT-01; BCI NCT 007005003  
Clintara LLC (Boston, MA)

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## **METHODOLOGICAL CHALLENGES IN A TWO-SITE RANDOMIZED, CONTROLLED TRIAL OF KETAMINE IN MAJOR DEPRESSION**

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The aim of this paper is to describe methodological issues pertaining to the use of a common depression rating scale, the Montgomery Asberg Depression Rating Scale (MADRS), in the context of a 2-site randomized clinical trial of intravenous ketamine in patients with treatment-resistant major depressive disorder. We explored whether protocol modifications to MADRS rating conventions would increase variance in depression outcomes by site.

73 adult patients across two academic sites were randomized to receive a single 40-minute sub-anesthetic dose infusion of either ketamine or midazolam (used as a psychoactive control) under double-blind conditions. Change in depression severity from baseline, as well as response rates, were evaluated at regular intervals (40 min, 120 min, 180 min, 240 min, 24 hr, 48 hr, 72 hr, Day 7) over a 7 day period. The primary efficacy endpoint was at 24 hours, with the MADRS selected as the primary outcome scale.

Protocol features impacting MADRS ratings included the following: (1) Instead of rating symptoms over a one week period, post-baseline symptoms were evaluated “since the last rating.” The interval between serial MADRS ratings over the 7 day post-infusion monitoring period accordingly ranged from 40 min to 4 days. (2) Individual MADRS items for sleep and appetite were carried forward from pre-infusion baseline scores for the MADRS ratings performed on the day of infusion. (3) To preserve masking, the rater present during the acute post-infusion monitoring period was shielded from the continuous rater who conducted baseline, 24-hour, and all subsequent MADRS ratings. Prior to study start, both sites received extensive training in the rating conventions required by the modified MADRS, and raters at each site achieved acceptable inter-rater reliability. Analyses of outcome as function of treatment included site as a covariate.

MADRS scores at the primary endpoint (24 hours) did not differ as a function of site ( $F(1,70) = 0.63$ ,  $p = 0.4312$ ). MADRS scores at Day 7 also did not differ as a function of site ( $F(1,66) = 1.81$ ,  $p = 0.1833$ ). In terms of categorical response outcomes, the response rate at 24 hours did not differ as a function of site (Exact  $P = 0.1883$ ). Finally, responders at Day 7 did not differ as a function of site (Exact  $P = 0.1071$ ). To our knowledge, this trial was the first multi-site investigation of IV ketamine in a depressed patient population. There appeared to be little evidence of differential outcomes by site for the primary outcome, MADRS, despite modifications to its standard administration. Research on optimal antidepressant signal detection for multi-center trials of ketamine and similar agents is necessary.

### **Learning Objectives:**

- Understand procedural safeguards necessary to ensure masking of primary efficacy outcome raters from the acute early side effects of ketamine.
- Apply the findings of exploratory research to help guide investigators in the management of future multi-site infusion studies of agents with psychoactive properties.
- Identify challenges in the assessment of rapid changes in depressive symptoms following treatment with ketamine.

### **Source of Funding:**

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#### **A RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF THE DOPAMINE- $\beta$ -HYDROXYLASE (DBH) INHIBITOR, NEPICASTAT, FOR THE TREATMENT OF PTSD IN OIF/OEF VETERANS: PRELIMINARY RESULTS**

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Clinical and preclinical studies have found a substantial increase in noradrenergic (NA) activity associated with the pathophysiology of posttraumatic stress disorder (PTSD). Recent clinical studies have shown improved PTSD hyper-arousal symptoms by using NA post-synaptic antagonists. Another therapeutic approach may be to inhibit the conversion of dopamine (DA) to norepineprine (NA) with a dopamine- $\beta$ -hydroxylase (DBH) inhibitor. In fact, PTSD symptoms were reduced after treatment with the weak DBH inhibitor, disulfiram, in a small clinical study. A more potent DBH-inhibitor, called nopicastat, is in early drug development and may offer potent anxiolytic effects.

Veterans of the US military with PTSD were enrolled in a multi-site, randomized, double-blind, placebo-controlled clinical trial of the nopicastat, monotherapy. Ninety-one Veterans who consented and met inclusion criteria were randomized to either nopicastat 120 mg/day vs. placebo (1:1) monotherapy for 6-weeks at 4 VA Medical Centers. The study participants were predominantly Veterans of the Iraq and Afghanistan wars; however, Veterans of other eras were included. The primary outcome was the PTSD hyper-arousal symptom cluster (DSM-IV criterion D) derived from the Clinician Administered PTSD Scale (CAPS). Secondary outcomes included the total CAPS score, CAPS subscore B (re-experiencing) and CAPS subscore C (avoidance). A mixed-effects linear regression analysis was performed comparing the change in CAPS scores between the two groups over the 6-week treatment period. The difference between week 6 and baseline was  $-4.7 \pm 7.8$  for the nopicastat group and  $-6.3 \pm 6.7$  for the placebo group on the CAPS-D primary outcome;  $-19.9 \pm 22.3$  for nopicastat and  $-22.2 \pm 17.2$  for placebo on CAPS total score;  $-5.9 \pm 8.9$  for nopicastat and  $-7.7 \pm 7.4$  for placebo on CAPS-B; and  $-9.2 \pm 10.2$  for nopicastat and  $-8.6 \pm 8.6$  for placebo on CAPS-C. There were no significant differences between drug and placebo in primary and secondary outcomes.

Strengths of the study include the use of a novel, well tolerated medication with a known mechanism of action and the double-blind placebo-controlled design. Limitations include the small sample size, short duration of treatment, and study population.

#### **Learning Objectives:**

- To describe a Phase II clinical trial examining the therapeutic efficacy of a dopamine- $\beta$ -hydroxylase (DBH) inhibitor, nopicastat, as a monotherapy for PTSD.
- To identify the therapeutic effect of a 6-week trial of nopicastat on the hyperarousal symptom cluster of PTSD in military veterans.

**Source of Funding:**

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**CENTRAL REVIEW OF THE ADAS-COG: IDENTIFICATION OF RATER-ERRORS IN ALZHEIMER'S DISEASE CLINICAL TRIALS**

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**Background:** An emerging concern in Alzheimer's disease (AD) clinical trials research is that administration or scoring errors on the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) may undermine clinical trial results (Kobak, 2010; Schafer et al., 2011). Although most clinical trials employ experienced raters who have completed study-specific training, research has shown that these raters still make errors when conducting study assessments (Veroff et al., 2010). Central review of ADAS-Cog administrations has been developed as a method for reducing rater error, however, data on the benefits of these programs are limited. This investigation focused on the impact of central review on rater error rates when administering the ADAS-Cog.

**Method:** 515 raters across 4 AD clinical trials participated in a central review program for at least 15 months. Raters met minimum pre-defined experience criteria and completed an ADAS-Cog training program prior to performing study administrations. Source documents from study administrations were submitted for central review by assessment scale specialists and were evaluated for errors in scoring, administration, and documentation, and for aberrant rating patterns. Identified errors/aberrant rating patterns were classified into pre-specified category types and raters were remediated for errors.

**Results:** Across the 4 studies, 1,929 ADAS-Cog administrations were reviewed and 873 errors/aberrant rating patterns were identified. The most frequent error types were: recording errors, (failure to document the subject responses; 45%), scoring errors (29%), and calculation errors (14%). Recording errors were most frequently found in the "Naming" subtest and scoring errors in the "Orientation" subtest. Calculation errors were distributed across all ADAS-Cog subtests. Following central review and remediation, there was a 12% decrease in overall rater-errors/aberrant rating patterns over the 15-month period studied and a 17% decrease in errors that specifically resulted in EDC scoring changes.

**Conclusion:** Even the most experienced raters can make errors when administering or scoring the ADAS-Cog. Central review programs can be beneficial for 1) identifying the common errors that raters make, which can then inform future training programs, 2) providing ongoing retraining of raters throughout a study, 3) ensuring the accuracy of data collected, and 4) reducing error rates over time. The reduction in error and improvement of data quality may enhance the possibility of identifying treatment effect, especially since most AD trials are designed to detect a 1.5 to 4 point drug-placebo difference over 6-18 months (Mohs et al, 1997; Schneider et al, 2009).

**Learning Objectives:**

- Describe the types of errors raters often commit when administering and scoring the ADAS-Cog in clinical trials
- Describe central rating review methods and identify benefits of this intervention

**Source of Funding:** N/A

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## VISUAL ATTENTIONAL BIASES FOR DYSPHORIC AND SOCIAL STIMULI IN AD PATIENTS WITH APATHY AND DEPRESSION

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**Background:** Apathy and depression, two of the most prevalent behavioural disturbances in Alzheimer's disease (AD), often contribute to decline in quality of life for patients and their families. Symptoms of apathy and depression may be difficult to assess, particularly as cognition deteriorates. Our team developed the Visual Attention Scanning Technology (VAST), an eye-tracker which enables real-time measurements of attention patterns towards competing visual stimuli. Previous results suggest that VAST has the ability to distinguish between non-demented depressed patients and healthy controls. Using VAST in the AD population for the first time, we explored an objective method of assessing symptoms of apathy and depression that does not rely on patient verbal skills or caregiver reports.

**Methods:** This is a cross-sectional study of patients with mild to moderate AD (NINCDS-ADRDA criteria; Mini-Mental Status Examination, MMSE>10). Participants were screened for significant depression (DSM-IV-TR) and apathy (Neuropsychiatric Inventory, NPI≥4). On a computer screen, participants were presented a series of 16 slides, each containing 4 images of different themes (2 neutral, 1 social, 1 dysphoric), interspersed with filler slides. Patients were allowed 10.5 seconds to view each slide while VAST software measured the length of time spent fixating on each image. Groups were compared using analysis of variance (ANOVA).

**Results:** Of the 27 AD patients (16 females, age=76.6±9.6, MMSE=22.8±3.0) included in this preliminary analysis, 14 had neuropsychiatric symptoms (NPS, 9 significant apathy, 5 significant depression) and 13 had neither of these symptoms (nonNPS). These patients had comparable age and MMSE and all tolerated study procedures well. There were no significant differences between apathetic and depressed patients for fixation duration on dysphoric ( $F=0.26$ ,  $p=0.62$ ) and social images ( $F=1.36$ ,  $p=0.27$ ). NonNPS patients fixated longer on social compared with neutral and dysphoric images ( $F=10.9$ ,  $p<<0.001$ ). Apathetic patients did not show preference for social compared with neutral images, though they did fixate longer on dysphoric images ( $F=10.1$ ,  $p=0.001$ ). Finally, depressed patients demonstrated a strong preference for dysphoric over neutral images ( $F=7.4$ ,  $p=0.008$ ). Higher depression scores on the NPI were correlated with increased time spent fixating on dysphoric images ( $r=0.45$ ,  $p=0.016$ ,  $n=27$ ).

**Significance:** These preliminary findings suggest that while apathetic and depressed patients did not view social and dysphoric images differently, VAST generated a unique attentional bias profile within each patient group. The results of this study will begin the development of a non-invasive, cost-effective and novel objective tool for evaluating severity of apathy and depression in AD and might have the potential to predict and monitor treatment response.

## Learning Objectives:

- to understand the potential of eye-tracking technology as an assessment apathetic and depressive symptoms in Alzheimer's disease
- to increase understanding of attention bias in apathy and depression in Alzheimer's disease patients

**Source of Funding:** Consortium of Canadian Centres for Clinical Cognitive Research  
Sunnybrook Health Sciences Centre

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**TAKE THE RATER CHALLENGE: LIVE CALIBRATION ON PSYCHOMOTOR SYMPTOMS**

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**Introduction** – Many rating scales contain observational items, which tend to have low interrater reliability. The Hamilton Depression Rating Scale (HAMD) contains two such items: psychomotor agitation and psychomotor retardation. Across research studies, these two items often have the lowest reliability of all 17 items of the scale (Cicchetti and Prusoff, 1983). Lack of standardization of these ratings contributes to outcomes assessment variability in clinical trials and may affect signal detection. The goal of this poster is to allow participants to practice rating these two items, compare their scores with Gold Standard (GS) expert scores, and to provide feedback to them about any rating discrepancies. This exercise should help standardize scoring of these items across the group of participants.

**Method** – Six brief (1-2 minutes) video vignettes will be available on a mobile web site for smart phones as well as two iPads available at the poster itself. Half of the vignettes will be illustrations of different levels of psychomotor agitation, and half of retardation. All vignettes will have GS scores, previously established by experienced senior clinicians who regularly do HAMD ratings and whose ICCs for these items are consistently above .85. Meeting attendees may choose to view one or more of the vignettes, apply the HAMD item rating scale (from 0 to 4), and rate the degree of psychomotor disturbance seen in the vignette. A real-time display will show iterative ICCs of agreement between the GS scores and participants as well as the frequencies of each rating score for each vignette. With every score submitted, this display will automatically update the group ICCs and item score frequencies. Once their score is submitted, the participant will be shown on their device (mobile phone or iPad) the GS score for that vignette with a brief rationale for the expert rating. Participants will also be asked three brief questions about their background and experience (discipline, number of HAMDs done in past year, if they have been a HAMD trainer).

**Results**– This interactive poster will assess the level of agreement among attendees on ratings of psychomotor agitation and retardation on the HAMD, educate participants on the rationale for the gold standard ratings, and improve standardization.

**Learning Objectives:**

- To test oneself in rating psychomotor agitation and retardation
- To learn how participants' ratings compare to Gold Standard ratings of these items

**Source of Funding:** N/A

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## **PHARMACOLOGY, SAFETY AND EFFICACY IN MAJOR DEPRESSIVE DISORDER OF CX-157, A REVERSIBLE INHIBITOR OF MONOAMINE OXIDASE A**

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<sup>1</sup>PPDi

CX-157 is a reversible inhibitor of monoamine oxidase A is being developed for major depression. PET imaging studies in humans have confirmed target engagement and reversible pharmacology. PK/PD relationships support a 125mg bid dosing schedule. The 125 mg bid formulation was tested in a tyramine challenge study and demonstrated no cardiovascular effect at tyramine doses up to 80mg. A large well-controlled safety and efficacy study in which 360 subjects with major depression that had responded unsatisfactorily to previous treatment were randomized evenly to active and matching placebo demonstrated CX157 was safe and well-tolerated, but did not meet it's primary efficacy endpoint. A post hoc band pass analysis suggested evidence of clinical efficacy.

### **Learning Objectives:**

- Understand considerations for developing a novel anti-depressant
- Understand factors contributing to the assay sensitivity of an anti-depressant safety and efficacy trial

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## **TREATMENT OF DEPRESSION WITH ONABOTULINUMTOXINA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL**

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Existing treatments for major depression are ineffective, or only partially effective for many patients. Developing novel antidepressant strategies would have a major impact on patient care. Converging lines of evidence suggest a role for facial expressions in the pathophysiology and treatment of mood disorders. To determine the antidepressant effect of botulinum toxin A treatment of glabellar muscles in subjects with major depressive disorder we conducted a double-blind, randomized, placebo-controlled trial. In an outpatient clinical research center, eighty-five subjects with DSM-IV major depression were randomized to receive either onabotulinumtoxinA(OBA) (29 units for females and 40 units for males) or saline injections into glabellar frown muscles. Subjects were rated at screening, 3 and 6 weeks. The primary outcome measure was the response rate, as defined by  $\geq 50\%$  decrease in score on the Montgomery-Asberg Depression Rating Scale (MADRS). Response rates at 6 weeks from the date of injection were 52% and 15% in the OBA and placebo groups, respectively (  $P < 0.0009$  ). The secondary outcome measure of remission rate ( $\geq 50\%$  decrease in MADRS score and final score of 10 or less) was 27% with OBA and 7% with placebo (  $P < 0.027$  ). Six weeks after a single treatment MADRS scores of subjects were reduced by 47% in those given OBA , and by 21% in those given placebo (  $P < 0.0004$  ). The effect size, as assessed by Cohen's  $d$ , was 0.59.

In the OBA group, the effortful frown score at the 6 week visit was significantly correlated with MADRS response (  $p < 0.02$ , Spearman correlation coefficient), and with MADRS remission (  $p < 0.03$ , Spearman correlation coefficient) ; lower 6 week frown scores correlated with lower MADRS scores, and higher remission rates.

This is the first randomized, double blind, placebo-controlled clinical trial to show that a single treatment of the glabellar region with OBA induces a strong and sustained alleviation of symptoms in a broadly defined group of people with major depression, including patients not regarded as treatment resistant. Our trial is the first to show statistical significance for remission of depression after a single treatment with OBA to the glabellar frown muscles.

Trial Registration: clinicaltrials.gov Identifier: NCT01556971

**Learning Objectives:**

- To determine the antidepressant effect of botulinum toxin A treatment of glabellar muscles in subjects with major depressive disorder we conducted a double-blind, randomized, placebo-controlled trial.
- To determine the antidepressant effect of botulinum toxin A treatment of glabellar muscles in a broadly defined group with major depressive disorder, including patients not regarded as treatment resistant.

**Source of Funding:** To determine the antidepressant effect of botulinum toxin A treatment of glabellar muscles in subjects with major depressive disorder irrespective of their resting frown.

**Literature References:**

- To determine the antidepressant effect of botulinum toxin A treatment of glabellar muscles in subjects with major depressive disorder irrespective of their resting frown.

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**ADJUNCTIVE L-METHYLFOLATE 15 MG: EFFECT IN DEPRESSED PATIENTS WHEN ASSESSED BY LEVELS OF BIOMARKER AND GENOTYPE**

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**Background and Objective:** Genetic or biological markers may increase the risk of major depressive disorder (MDD) or inadequate response to therapy. The objective of this analysis was to evaluate the effect of specific markers alone and in combination on the antidepressant efficacy of adjunctive L-methylfolate 15 mg versus placebo added to SSRIs from a trial of inadequate responders to SSRIs.

**Methods:** This was a double-blind, randomized, placebo-controlled trial using the sequential parallel comparison design (SPCD). Outpatients with MDD and SSRI-resistant depression received L-methylfolate 15 mg/day for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/day for 30 days or placebo for 60 days. The effects of biological and genetic markers individually and combined on treatment response were evaluated.

**Results:** Seventy-five patients were enrolled. Patients with a BMI  $\geq 30$  kg/m<sup>2</sup> had significantly greater symptom reduction with L-methylfolate versus placebo ( $p=0.001$ ), as did patients with levels of hsCRP ( $p=0.05$ ) and 4-HNE ( $p\leq 0.003$ ) above the median, and SAM/SAH ratio below the median ( $p=0.005$ ). Average mean changes from baseline for HDRS-28 with combinations of these biomarkers plus MTHFR C677T, MTR 2756 AG/GG or MTRR 66 AG/GG polymorphisms were significantly greater with L-methylfolate vs. placebo (all  $p\leq 0.003$ ). Average mean changes from baseline for HDRS-28 with combinations of MTHFR C677T plus MTR 2756 AG/GG and MTR 2756 AG/GG plus MTRR 66 AG/GG were significant ( $p<0.001$ ).

**Conclusion:** Surrogate biomarkers or genomic markers associated with L-methylfolate synthesis and metabolism may identify patients with SSRI-resistant MDD who are responsive to adjunctive therapy with 15 mg L-methylfolate.

**Learning Objectives:**

- Identify the effect of treating symptoms of depression in patients with abnormalities in genotypic and biological markers.
- Recognize that addressing underlying metabolic dysfunction may result in improvement of core symptoms of depression.

**Source of Funding:** This work was supported by research grants from PamLab Inc., Covington, Louisiana

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## **DELAYING THE PROGRESSION OF DRIVING IMPAIRMENT IN INDIVIDUALS WITH MILD ALZHEIMER'S DISEASE**

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**Objectives:** To determine whether treatment with memantine delays the progression of driving impairment in patients with mild Alzheimer's Disease. Slowing the progression of driving impairment in this population may extend the quality of life of those with Alzheimer's Disease and ease the burden on their caregivers. If we can demonstrate a significant delay in the decline in driving ability, this could extend their driving time and therefore be of immense benefit to patients and their caregivers.

**Methods:** A sample of 60 otherwise healthy men and women 60 years and older with mild (Mini Mental State Exam-MMSE  $\geq$  23) Alzheimer's Disease was randomized at a 1:1 ratio in a double-blind, placebo controlled, 12 month trial of memantine titrated to a target dose of 20mg/day versus placebo. Subjects with poor vision and depression were excluded. Driving ability was measured by actual driving (on the road driving test) and cognitive performance on a battery of neuropsychological assessments testing abilities necessary for driving (executive functioning, visuospatial abilities, attention, orientation and tests designed to measure driving ability in older adults). The primary outcome measure is the number of subjects in each group who are able to pass the DriveABLE test at month 12 (endpoint). The secondary outcome measures are the change from baseline to endpoint on driving related measures. Outcome measures (scores from DriveABLE-On Road Test and cognitive assessments) were acquired at baseline, 6-months, and 12 months. Cognitive assessments included ADAS-Cog, Trail Making Tests A & B, Rey-Osterrieth Complex Figure Test, Useful Field of Vision, and the Motor Free Visual Perception Test - Visual Closure Subtest.

**Results:** 43 subjects were randomized. Preliminary analysis showed efficacy for memantine delaying progression of driving impairment. At 12 months 100% of the treatment group either stayed the same or improved their driving ability, while only 75% of the placebo group did the same or better ( $p=.04$ ). Controlling for baseline ability, the difference between the treatment groups at 12 months was significant for the Rey-Osterrieth Complex Figure Test,  $F(2,23) 4.16, p=.05$ . Least squares means for the treatment group were 30.41 versus 27.39 for the placebo control. Similarly, the placebo control group required more time to complete Trails B and made more errors at 12 months than did the treatment group although the difference did not reach statistical significance.

**Conclusion:** In this preliminary analysis, addition of memantine to the drug regimen appears to have efficacy in delaying driving impairment in subjects with mild Alzheimer's Disease.

### **Learning Objectives:**

- To understand the impact that Alzheimer's Disease has on Driving Ability.
- To learn how memantine may delay driving impairment in patients with mild Alzheimer's Disease.

**Source of Funding:** Forest Research Institute

**Literature References:**



- Alzheimer's Association. 2012 Alzheimer's disease facts and figures. Alzheimer's and Dementia: The Journal of the Alzheimer's Association. March 2012; 8:131–168.
- “When should drivers with Alzheimer’s disease turn over the keys?” (2012) Neurology Reviews 20(11): 9.

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## A SINGLE-DOSE PHARMACOKINETIC STUDY OF LEVOMILNACIPRAN SR IN SUBJECTS WITH NORMAL AND IMPAIRED HEPATIC FUNCTION

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**Objective:** Levomilnacipran (1*S*, 2*R*-milnacipran), is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with approximately 2-fold greater potency for reuptake inhibition of norepinephrine relative to serotonin. Levomilnacipran is in late-stage clinical development for the treatment of major depressive disorder in adults; a sustained release (SR) formulation was developed for once-daily dosing. Hepatic elimination of levomilnacipran is low. The objective of this study was to evaluate the pharmacokinetic (PK) characteristics and safety profile of levomilnacipran SR in subjects with impaired and normal hepatic function.

**Methods:** A single-dose, open-label, parallel-group study in 32 males and females (age 33-66 years) was conducted. Subjects were categorized into 4 groups (8 subjects each): normal, mild (Child-Pugh A), moderate (Child-Pugh B), severe (Child-Pugh C; no patients had scores >13) hepatic impairment. Subjects with normal hepatic function were age-, weight-, and gender-matched to subjects with hepatic impairment. All subjects received a single oral dose of levomilnacipran SR 40 mg with 240 mL of water on Day 1 under fed conditions. PK blood samples (predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96 hours postdose) and urine samples (predose, 0-4, 4-8, 8-12, 12-16, 16-32, 32-48, 48-72, 72-96 hours postdose) were collected and analyzed using validated liquid chromatography-mass spectrometry methods. Descriptive statistics were provided by group for PK parameters;  $C_{max}$  and AUC were compared using a linear mixed effects model with hepatic function group as a fixed effect. Safety assessments included adverse events, laboratory evaluations, vital sign assessments, ECGs, and C-SSRS.

**Results:** All subjects completed the study. Following a single dose of levomilnacipran SR 40 mg, mean (SD) values for  $C_{max}$  [ng/mL] in subjects with normal function, and mild, moderate or severe hepatic impairment were 59.72 (9.00), 76.82 (19.65), 64.82 (11.43), 77.04 (14.01), respectively; for  $AUC_{0-\infty}$  [h•ng/mL] values were 1787.68 (598.09), 1853.79 (822.92), 1940.72 (599.00), 2324.50 (598.58), respectively; and for  $T_{1/2}$  [h] values were 15.60 (9.01), 12.80 (3.45), 15.85 (4.00), 15.96 (3.70), respectively. For  $AUC_{0-\infty}$ , ratio of geometric means (90% CI) for hepatically impaired versus normal subjects was 98.78% (73.56-132.65) for mild, 108% (80.96-146.00) for moderate, and 131.80% (98.15-177.00) for severe hepatic impairment. Overall safety profiles in normal and hepatic impairment groups were not meaningfully different. No notable changes were observed in ECG, laboratory tests, or vital sign parameters.

**Conclusions:** Single-dose levomilnacipran 40 mg was generally well tolerated in healthy subjects and patients with hepatic impairment; an approximate 32% increase in levomilnacipran exposure was observed in patients with severe hepatic impairment. Levomilnacipran SR dose adjustment is not necessary in patients with mild, moderate, or severe hepatic impairment.

### Learning Objectives:

- At the conclusion of this session, the participant should be able to evaluate the pharmacokinetics of levomilnacipran SR in patients with hepatic impairment.
- At the conclusion of this session, the participant should be aware that no levomilnacipran SR dose adjustment may be necessary for patients with mild, moderate, and severe hepatic impairment.

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

### Literature References:

- US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact of Dosing and Labeling. May 2003.
- Anderson PO, Knoben JF, editors. Handbook of Clinical Drug Data, 8th ed. Hamilton, IL: Drug Intelligence Publications; 1998. p 906.

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## **GEPIRONE-ER: EFFECTIVE TREATMENT OF MAJOR DEPRESSION AND ACCOMPANYING SEXUAL DYSFUNCTION**

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**Specific purpose:** To improve treatment outcome in major depression.

**Background:** Current treatments of Major Depression do not take into consideration the 80% of depressed subjects who have sexual dysfunction at baseline. Only 30% of treated depressed subjects attain remission. Current treatments of depression do not improve sexual function. In fact, the Serotonin Reuptake Inhibitors (SSRIs) and the Serotonin Nor-epinephrine Reuptake Inhibitors (SNRIs) further compromise sexual function. There have been no approved pharmacologic treatments or combinations of treatments that will improve both depression and sexual dysfunction. Gepirone-ER, a 5-HT<sub>1A</sub> agonist may achieve successful treatment of Major Depression and Sexual Dysfunction.

**Methods:** In 5 studies of Major Depression, major depression was diagnosed by DSM-IV criteria and depression measured by the Hamilton Rating Scale for Depression (HAM-D). Sexual function was measured in 4 studies by the Derogatis Inventory of Sexual Function (DISF or DISF-SR self report)

**Results:** Two studies of Gepirone-ER in Major Depression subjects showed statistically significant antidepressant activity as measured by the HAM-D-17 change from baseline. Study 134001 HAM-D-17 effect size -2.47, p=0.013, and FKGBE007 effect size -2.45, p=0.018. These two studies did not have SSRI comparators and only 134001 had sexual function measurements. DISF results for 134001 gepirone-ER treated vs. placebo men and women combined are DISF total score effect size +6.1, p=0.017, and DISF desire domain effect size +2.3, p=0.043.

Four studies pooled show positive effects for gepirone-ER on sexual function. DISF change from baseline total scores were gepirone-ER 5.33 (p=0.04 better than placebo), fluoxetine (only 2 studies) -4.25 (p=0.01 worse than placebo) and placebo 1.73.

**Conclusions:** Sexual dysfunction is an integral part of major depression and must be considered in the treatment of major depression. Gepirone-ER, effective in both major depression and sexual dysfunction, should allow a rational and effective treatment of this illness, perhaps increasing remission rate.

### **Learning Objectives:**

- To recognize the prevalence and importance of sexual dysfunction in Major Depression
- To describe a potential new treatment of Major Depression and Sexual Dysfunction

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## **EARLY IMPROVEMENT AND SUSTAINED RESPONSE WITH VILAZODONE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER POOLED ANALYSES FROM 2 PHASE III TRIALS**

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**Background:** In patients with major depressive disorder (MDD), robust and early improvement of symptoms with antidepressant therapy is associated with better treatment outcomes and longer-term response and remission. Vilazodone, a serotonin reuptake inhibitor and 5-HT<sub>1A</sub> receptor partial agonist, is approved by the US Food and Drug Administration for treatment of MDD in adults. Post hoc analyses using data from 2 positive, placebo-controlled trials evaluated sustained response with vilazodone in patients with MDD.

**Methods:** Post hoc analyses were carried out using data from two positive 8-week, double-blind, placebo-controlled trials (NCT00285376 and NCT00683592). Both trials were of similar design comprising adult

patients with DSM-IV-TR–defined MDD. Patients randomized to vilazodone were titrated to a target dose of 40 mg (10 mg QD for 2 days, 20 mg QD for the next 7 days and 40 mg QD thereafter), taken once daily with food. The primary efficacy assessment in both trials was the Montgomery-Asberg Depression Rating Scale (MADRS). Post hoc pooled analyses evaluated the proportion of patients and the associated odds ratio (OR) for achieving sustained response (defined as having  $\geq 50\%$  change from baseline in MADRS score at the last 2 visits of double-blind treatment) and early sustained response (meeting response criteria at Week 1 or 2 and at last 2 visits of double-blind treatment). These analyses were repeated using increasingly stringent response thresholds ( $\geq 50\%$  improvement and MADRS total score  $\leq 16$ ,  $\leq 14$ , and  $\leq 12$ ). Sustained response and early sustained rates were analyzed using a logistic regression model with treatment group and corresponding MADRS baseline value as explanatory variables.

**Results:** The Intent-to-Treat Population comprised 432 placebo-treated patients and 431 vilazodone-treated patients who had  $\geq 1$  postbaseline MADRS assessment. Baseline MADRS scores were 31.4 in both treatment groups. Vilazodone-treated patients compared with placebo were more likely to demonstrate early sustained response (9% vs 4%; OR=2.29;  $P=.005$ ); this remained true when all MADRS early sustained response criteria were used:  $\leq 16$  (9% vs 4%, OR=2.29,  $P=.005$ );  $\leq 14$  (7% vs 4%, OR=2.16,  $P=.017$ );  $\leq 12$  (6% vs 3%, OR=2.47,  $P=.014$ ). At the end of study, significantly more vilazodone- versus placebo-patients met sustained response criteria (32% vs 22%, OR= 1.65,  $P=.001$ ). Vilazodone treatment remained significantly superior versus placebo on sustained response even when increasingly stringent MADRS response cutoffs were used:  $\leq 16$  (31% vs 21%, OR=1.66,  $P=.001$ );  $\leq 14$  (28% vs 19%, OR=1.66,  $P=.002$ );  $\leq 12$  (25% vs 17%, OR=1.65,  $P=.003$ ).

**Discussion:** Significantly more vilazodone patients compared with placebo patients showed early sustained and sustained response.

#### **Learning Objectives:**

- Evaluate the efficacy of vilazodone treatment in achieving sustained response in patients with major depressive disorder
- Evaluate measures of early and sustained improvement in patients treated with vilazodone.

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

#### **Literature References:**

- Khan A, Cutler AJ, Kajdasz DK, Gallipoli S, Athanasiou M, Robinson DS, Whalen H, Reed CR: A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. *J Clin Psychiatry* 2011; 72; 442-447.
- Rickels K, Athanasiou M, Robinson DS, Gibertini M, Whalen H, Reed CR: Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*; 2009; 70; 326-333.

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### **A RANDOMIZED, DOUBLE-BLIND, STUDY OF VORTIOXETINE VERSUS AGOMELATINE IN ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD) SWITCHED AFTER INADEQUATE RESPONSE TO SSRI OR SNRI TREATMENT**

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<sup>1</sup>H. Lundbeck A/S

**Background:** The investigational antidepressant vortioxetine (Lu AA21004) is a multimodal 5-HT<sub>3</sub>, 5-HT<sub>7</sub> and 5-HT<sub>1D</sub> receptor antagonist, 5-HT<sub>1B</sub> receptor partial agonist, 5-HT<sub>1A</sub> receptor agonist and inhibitor of the 5-HT transporter [1]. Data from randomized trials comparing treatment strategies in patients who were unresponsive to first-line antidepressant treatment are limited. In the large open-label STAR\*D study in which patients received treatment with citalopram (level 1) and non-responders were randomly switched to a second treatment (level 2), the mean remission rate after 12-14 weeks was 30.6% [2].

**Objectives:** To compare efficacy and tolerability of flexible-dose treatment with vortioxetine *versus* agomelatine in patients with MDD who presented with an inadequate response to SSRI/SNRI monotherapy and wanted to switch treatment and would benefit, in the investigator's clinical opinion.

**Methods:** Randomized, double-blind comparator study (NCT01488071). Primary efficacy endpoint was the change from baseline to Week 8 in MADRS total score in the full-analysis set (FAS) analysed by MMRM using a non-inferiority test. Secondary endpoints included assessment of remission (MADRS total score  $\leq 10$ ), anxiety symptoms (HAM-A), global clinical judgment (CGI), and overall functioning (SDS).

**Results:** Eligible patients were randomized (1:1) to vortioxetine (10-20mg/day) or agomelatine (25-50 mg/day) for 12 weeks of double-blind treatment. On the primary efficacy endpoint, vortioxetine (n=252) was statistically significantly superior to agomelatine (n=241) ( $p < 0.05$ ) by 2.2 MADRS points. Significant differences in favour of vortioxetine were found for the MADRS, HAM-A, CGI-S, CGI-I, and SDS from Week 4 onwards (FAS, MMRM;  $p < 0.05$ ) and robustness was confirmed by significant differences by ANCOVA (FAS, LOCF). Remission rates for vortioxetine *versus* agomelatine (LOCF) were 40.5% *versus* 29.5% ( $p = 0.0054$ ) at Week 8 and 55.2% *versus* 39.4% ( $p = 0.0002$ ) at Week 12. Fewer patients withdrew due to adverse events with vortioxetine (5.9%) than agomelatine (9.5%). Adverse events with the highest incidence were nausea, headache, dizziness and somnolence.

**Conclusions:** The primary efficacy endpoint of this comparator study was met, with vortioxetine also showing a significant benefit compared to agomelatine in difficult to treat MDD patients who directly switched antidepressant treatment after an inadequate response to SSRI/SNRI treatment. Statistically significant differences were seen from Week 4 onwards. The vortioxetine remission rate after 8 and 12 weeks was higher than in the STAR\*D study. Thus, vortioxetine was both efficacious and well-tolerated.

[1] Bang-Andersen B, et al. J Med Chem 2011;54:3206-21.

[2] Rush AJ, et al. Am J Psychiatry 2006;163:1905-17.

#### **Learning Objectives:**

- At the conclusion of this session, the participant should understand that in MDD patients with an inadequate response to SSRI/SNRI treatment, subsequent switch to either vortioxetine or agomelatine resulted in clinically relevant improvement after 8 to 12 weeks of treatment.
- In this difficult to treat patient group, vortioxetine showed a significant benefit versus agomelatine on the primary efficacy endpoint and on most secondary efficacy endpoints as early as Week 4.

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#### **CLINICALLY MEANINGFUL RESPONSE IN SEVERE MAJOR DEPRESSIVE DISORDER: ANALYSIS OF CORRELATION BETWEEN CGI-I AND MADRS FROM PHASE II STUDY WITH AZD6765**

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**Objective:** AZD6765 is a low-trapping NMDA channel blocker in development as adjunctive treatment for patients with severe MDD and a history of inadequate response to multiple prior treatments. In a Phase II study, patients treated with AZD6765 (100 or 150 mg, 3 IV infusions/week to Week 3, with 5-week follow up) showed significantly greater change from baseline to Week 3 in MADRS score vs placebo. By Week 3 significant improvement vs placebo was also seen in MADRS response (ie, reduction  $\geq 50\%$ ) for AZD6765 (100 mg) and in CGI-I rating for AZD6765 (both doses). During follow up, MADRS score differed significantly between AZD6765 100 mg and placebo for 2 weeks. Treatment response should be determined based on the patient population and, to define a more clinically meaningful MADRS response, we propose a methodology using the CGI-I scale to calibrate clinically important improvement in this patient population.

**Methods:** Receiver-operating curve analysis aligned CGI-I scores with symptomatic change measured by MADRS. A CGI-I score of 1 or 2 (ie, clinician rating of much or very much improved) was used to measure “true” response and different MADRS cutoffs (absolute MADRS score: 5-35, %MADRS score change: 20-55%) were systematically examined for thresholds that conjointly minimized false-positive

and false-negative prediction errors. Importantly, initial alignment between MADRS and CGI-I was performed independently of drug treatment grouping.

**Results:** High correlations ( $>0.82$ ) were observed between CGI-I score and both %MADRS change and MADRS total score at Week 3. The most reliable predictors of CGI-I response were  $\geq 35\%$  reduction in MADRS and/or MADRS score  $\leq 20$ . The proposed methodology provided a better and systematic way to calibrate clinical benefit in the studied patient population, capable of improving the sensitivity to detect sustained durable benefit of treatment. The proportion of patients with a CGI-I score  $\leq 2$  was significantly higher with AZD6765 100 mg than placebo from 3-8 weeks.

**Discussion:** CGI-I is a valid indicator of clinically meaningful response sufficient to calibrate treatment definition of response based on a disorder-specific rating scale (MADRS). This research provides support that, for the severe, treatment-refractory MDD population, clinically meaningful response is observed at higher MADRS scores than in the conventional MDD population and different criteria are warranted.

#### **Learning Objectives:**

- Understand relationship between a disorder-specific rating scale (MADRS) and clinical judgment of patient improvement (CGI-I) in a severe, difficult to treat patient population.
- Demonstrate how CGI-I and MADRS criteria can be applied to measure sustained and clinically meaningful response based on 3-week treatment with AZD6765.

**Source of Funding:** AstraZeneca

#### **Literature References:**

- Sanacora G, Smith MA, Pathak S, et al. Adjunctive AZD6765, a low-trapping NMDA channel blocker, in treatment-resistant major depressive disorder: A randomized, placebo-controlled study. *Neuropsychopharmacology* 2012; 38:S211; T28.
- Riedel M, Möller H-J, Obermeier M, et al. Response and remission criteria in major depression - a validation of current practice. *J Psychiatr Res* 2010; 44:1063-68.

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### **A PHASE II RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF GLYX-13 FOR THE RAPID TREATMENT OF MAJOR DEPRESSIVE DISORDER USING CENTRAL RATINGS**

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#### **Introduction**

NMDA receptor ligands have been shown to rapidly treat depression but are associated with psychotomimetic effects. GLYX-13 is an NMDA receptor glycine site functional partial agonist with ~25% of the agonist activity of glycine or D-serine. Animal models suggest a single intravenous dose may produce long-term efficacy without psychotomimetic effects. A phase II randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy of GLYX-13 with Central Raters. The current study examines the effects of a single dose of GLYX-13 in subjects with inadequate response to previous treatment for MDD.

#### **Methods**

48 male and 68 female subjects received a single dose of GLYX-13 (1-/5-/10-/30-mg/kg) or placebo. Central Raters assessed subjects via telephone using the HDRS-17 at Screening, Baseline, Days 1, 3, 7, 14, 21 and 28.

#### **Results**

The *a priori* primary efficacy ANCOVA on pooled drug dose versus placebo was not significant for change from baseline to Day 1 on HDRS-17 total score. MMRM revealed a statistically significant reduction in HDRS-17 total score versus placebo at Day 3 for 5-mg/kg (-4.4;  $p<.05$ ) and a trend at Day 1 for 5-mg/kg (-3.5;  $p=.068$ ) and at Day 7 for 5 and 10-mg/kg (-4.0 for both;  $p$ 's=.059 and .073). GLYX-13 did not cause psychotomimetic side effects at any dose studied.

## Conclusion

This study suggests that GLYX-13, an NMDA receptor glycine site functional partial agonist, rapidly reduces depression scores without eliciting psychotomimetic effects at therapeutic doses as assessed by Central Raters. Further study is indicated.

## Learning Objectives:

- To understand the effects of a single intravenous dose of GLYX-13 in subjects with inadequate response to previous treatment for MDD.
- To understand methodological concerns specific to assessing rapid onset anti-depressants.

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

## Literature References:

- Burch RM, Singla N, Parulan C, Burgdorf J. GLYX-13, an NMDA receptor glycine site functional partial agonist, does not elicit psychotomimetic side effects in normal human volunteers at doses expected to be therapeutic in treatment-resistant major depressive disorder. Presented at: The 50th Annual Meeting of the National Clinical Drug Evaluation Unit (NCDEU); 2010 June 14 – 17; Boca Raton, Florida.
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## A PRAGMATIC MEGATRIAL TO OPTIMISE THE FIRST- AND SECOND-LINE TREATMENTS FOR PATIENTS WITH MAJOR DEPRESSION: SUN(^\_^)D STUDY PROTOCOL AND INITIAL RESULTS

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**Background:** After more than half a century of modern psychopharmacology, we did not know which antidepressant to use as first line treatment. The recently published multiple-treatments meta-analysis of 12 new generation antidepressants has provided some partial answers to the question. However, because more than half of the patients with major depression starting treatment do not remit after adequate trial with the first agent, they will need a second line treatment. Dose escalation, augmentation and switching are the three often recommended second line strategies but we do not know which is the best. Starting with these findings, this trial aims to establish the optimum 1st line and 2nd line antidepressant treatment strategy among adult patients with a non-psychotic unipolar major depressive episode.

**Methods:** SUN(^\_^)D, the Strategic Use of New generation antidepressants for Depression, is an assessor-blinded, parallel-group, multi-center randomized controlled megatrial (n=2000). Step I is a cluster-randomized trial comparing titration up to the minimum vs. maximum of the recommended dose range among patients starting with sertraline. The primary outcome is the change in the Patient Health Questionnaire (PHQ)-9 scores administered by a blinded rater via telephone at week 1 through 3. Step II is an individually randomized trial comparing staying on sertraline, augmentation of sertraline with mirtazapine, and switching to mirtazapine among patients who have not remitted on the first line treatment by week 3. The primary outcome is the change in the PHQ-9 scores at week 4 through 9. Step III represents a continuation phase to Steps I and II and aims to establish longer-term effectiveness and acceptability of the above-examined treatment strategies up to week 25.

**Results & Conclusions:** Despite this rather complex trial design, its running has been smooth. The trial is now run in eight regional centers across Japan consisting of 45 clinics/hospitals, recruiting ca. 50 patients

a month. The follow-up rates have been 97%, 96% and 97% at weeks 3, 9 and 25 respectively. The trial promises to be a pragmatic large trial to answer important clinical questions that every clinician treating patients with major depression faces in his/her daily practices concerning its first- and second-line treatments.

#### **Learning Objectives:**

- To understand the design and initial results of the largest trial of pharmacotherapy for depression ever conducted in Japan.
- To understand the feasibility and limitations of a pragmatic megatrial.

**Source of Funding:** The trial is supported by the Grant-in-Aid by the Ministry of Health, Labour and Welfare, Japan and the Japan Foundation for Neuroscience and Mental Health.

#### **Literature References:**

- Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, Watanabe N, Nakagawa A, Omori IM, McGuire H, Tansella M & Barbui C: Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; 373:746-758
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### **ANTI-ANHEDONIC EFFECTS OF KETAMINE AND ITS NEURAL CORRELATES IN BIPOLAR DEPRESSION**

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Almost 40% of patients with depression suffer from clinically significant anhedonia (Pelizza & Ferrari), the loss of enjoyment or desire towards a previously pleasurable activity. Critically, these patients have poorer treatment prognosis than their non-anhedonic counterparts (Spijker et al., 2001). Accumulating evidence suggests that standard treatments for depression have little efficacy in treating anhedonic symptomatology (Price et al., 2009); there is currently no FDA approved treatment for anhedonia. The noncompetitive NMDA receptor antagonist ketamine has shown remarkable consistency in rapidly ameliorating depressive symptoms in both unipolar and bipolar depression (Zarate et al., 2006; Zarate et al., 2012). However, it is unknown whether ketamine also possesses an anti-anhedonic function.

In a randomized double-blind placebo-controlled crossover study, we assessed ketamine's anti-anhedonic effects in a sample of 26 treatment-resistant patients diagnosed with bipolar disorder. We evaluated levels of anhedonia using the Snaith-Hamilton Pleasure Scale (SHAPS). In a subsample of these patients (N=21) we also measured the neural response to both placebo and ketamine infusion using [18 F] fluorodeoxyglucose positron emission tomography (PET). We regressed changes in anhedonia levels onto difference images to identify mediating effects of ketamine's anti-anhedonic capacity. Finally, we assessed the neurobiology of anhedonia by correlating scores on the SHAPS at the time of the PET scan with glucose metabolism. Our analyses comprised both a region of interest (ROI) approach, focused on the pleasure network (ventral striatum and orbitofrontal cortex), and also a whole brain investigation. Our results indicate that levels of anhedonia were significantly reduced following ketamine in comparison to placebo (main effect of drug,  $t=2.023$ ,  $p=.043$ ). This reduction lasted from 40 minutes to 7 days, following one infusion. Our PET analyses indicate a role for ventral striatum in ketamine's anti-anhedonic response ( $r=-.48$ ,  $p=.036$ ); individuals with the largest increase in metabolism in ventral

striatum had the highest anti-anhedonic response. Finally, we evidence state relationships between levels of anhedonia post-ketamine and post-placebo. Notably, following ketamine, we found heightened activity in the posterior cingulate ( $P_{\text{corrected}} = .009$ ) positively correlated with levels of anhedonia, while decreased levels of anhedonia were found to be associated with greater amygdalae and insular glucose metabolism ( $P_{\text{corrected}} = .007$ ).

Our results add increasing weight to the potential for NMDA receptor antagonists in treating depression. Importantly, anhedonia has been targeted as a tractable endophenotype for the heterogeneous depression classification; elucidating the neural mechanisms behind both the endophenotype and its treatment are critical stepping-stones for progress in psychiatry outlined in the Research Domain Criteria (Insel et al., 2010).

#### **Learning Objectives:**

- To evaluate if ketamine has an anti-anhedonic effect
- To establish the neural correlates of both the anti-anhedonic effect of ketamine and also anhedonia

**Source of Funding:** National Institute of Health Intramural Research Program

#### **Literature References:**

- <http://www.ncbi.nlm.nih.gov/pubmed/22177980>
- <http://www.ncbi.nlm.nih.gov/pubmed/20603146>

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### **SAFETY AND TOLERABILITY OF LEVOMILNACIPRAN SR IN MAJOR DEPRESSIVE DISORDER: ANALYSIS OF 5 SHORT-TERM, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS**

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**Objective:** Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with approximately 2-fold greater in vitro potency for reuptake inhibition of norepinephrine than serotonin. Levomilnacipran is in late-stage clinical development for the treatment of major depressive disorder (MDD) in adults; a sustained release (SR) formulation was developed for once-daily dosing. This integrated summary evaluated the safety and tolerability profile of levomilnacipran SR in short-term MDD studies.

**Methods:** Data from 5 randomized, double-blind, placebo-controlled trials were analyzed: 2 flexible-dose (40-120 mg/d) and 2 fixed-dose (40, 80, 120 mg/d and 40, 80 mg/d), 8-week, US trials and 1 flexible-dose (75-100 mg/day), 10-week, non-US trial. Patients were 18-80 years of age and met DSM-IV-TR criteria for MDD. Safety evaluations included adverse events (AEs), clinical laboratory tests, vital signs, ECGs, and the Columbia-Suicide Severity Rating Scale (C-SSRS; 4 US studies only). Analyses were based on the Safety Population (all patients who received at  $\geq 1$  dose of levomilnacipran SR); descriptive statistics were provided.

**Results:** Demographic and baseline characteristics were similar between levomilnacipran SR (n=1583) and placebo (n=1040) groups; 75% of levomilnacipran SR and 80% of placebo patients completed the trials. Treatment-emergent AEs (TEAEs) were reported in 77% and 61% of levomilnacipran SR and placebo patients, respectively. The most frequent TEAEs ( $\geq 5\%$  and twice placebo) for levomilnacipran SR vs placebo were nausea (17% vs 6%), constipation (9% vs 3%), hyperhidrosis (9% vs 2%), heart rate increased (6% vs 1%), erectile dysfunction (6% vs 1% of males), tachycardia (5% vs 1%), vomiting (5% vs 1%), and palpitations (5% vs 1%). No deaths were reported; the incidence of serious AEs was similar between treatment groups (1%). In general, incidence of AEs was not dose related. Discontinuations due to AEs occurred in 3% of placebo and 9% of levomilnacipran SR patients. Suicidality TEAEs were low and similar in both groups. C-SSRS-rated suicidal ideation was reported in 22% of placebo and 24% of levomilnacipran SR patients; suicidal behavior was reported in  $<1\%$  of patients in both groups. Mean



changes from baseline in systolic BP, diastolic BP, and heart rate were +3.0 mmHg, +3.2 mmHg, and +7.4 bpm for levomilnacipran SR, and -0.4 mmHg, no change, and -0.3 bpm for placebo, respectively. There was a dose-dependent mean increase in QTcB interval in levomilnacipran SR patients and a mean decrease in placebo patients; mean changes in QTcF interval were small and similar between groups. No clinically significant effects on body weight or laboratory tests were reported.

**Conclusions:** Data from 5 double-blind trials indicate that levomilnacipran SR has a favorable safety and tolerability profile.

**Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the safety and tolerability profile of levomilnacipran SR in the treatment of major depressive disorder based on the findings of 5 randomized, placebo-controlled, double-blind trials.
- At the conclusion of this session, the participant should be able to identify common treatment-related adverse events and changes in clinical parameters associated with levomilnacipran SR.

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

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**DESVENLAFAXINE IS NEITHER A PERPETRATOR NOR A VICTIM OF DRUG-DRUG INTERACTIONS MEDIATED BY CYTOCHROME P450 2D6 OR 3A4**

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**Background:** Patients on antidepressants are frequently on multiple concomitant medications,<sup>1</sup> putting them at risk for drug-drug interactions (DDIs).<sup>2</sup> For this reason, a series of studies was undertaken to assess the risk for clinically meaningful DDIs involving desvenlafaxine and substrates or inhibitors of cytochrome P450 (CYP) enzymes 2D6 and 3A4.

**Methods:** Seven studies tested the effects of steady-state treatment with fixed doses of desvenlafaxine (ranging from 50 to 400 mg/d) on the pharmacokinetics (PK) of two CYP 2D6 model substrate drugs (desipramine and tamoxifen), one CYP 3A4 model substrate drug (midazolam), and one drug nearly equally a substrate for CYP 2D6 and CYP 3A4 (aripiprazole). An eighth study examined the effect of the substantial CYP 3A4 inhibitor ketoconazole (200 mg twice daily for 8 days) on desvenlafaxine 400 mg PK.

**Results:** Desvenlafaxine coadministration had minimal effect on CYP 2D6 or 3A4 substrate drug exposure, measured either by peak plasma concentration ( $C_{max}$ ) or the area under the plasma concentration versus time curve (AUC).

Substrate drug Metabolite	Desvenlafaxine dose	Change in $C_{max}$	Change in AUC
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Desipramine	100 mg/d	25–30%	17–36%
	400 mg/d	52%	90%
Tamoxifen	100 mg/d	↓<1%	<1%
Endoxifen*	100 mg/d	↓8%	↓12%
Midazolam	50 mg/d	↓14%	↓29%
	400 mg/d	↓16%	↓31%
Aripiprazole	100 mg/d	1%	6%
* active metabolite produced by CYP 2D6 mediated biotransformation of tamoxifen			

Coadministration with ketoconazole increased the  $C_{max}$  and AUC of 400 mg of desvenlafaxine by 8% and 43%, respectively.

**Conclusions:** Based on these results, desvenlafaxine is neither a perpetrator nor victim of a clinically meaningful DDI mediated by either CYP 2D6 or CYP 3A4.

#### **Learning Objectives:**

- To recognize that desvenlafaxine has minimal potential for DDIs with CYP2D6 or CYP3A4 substrates.
- To understand that drugs that substantially inhibit CYP3A4 have minor impact on the pharmacokinetics of desvenlafaxine.

**Source of Funding:** Sponsored by Pfizer

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### **QUALITATIVE DEVELOPMENT AND COGNITIVE EVALUATION OF THE SYMPTOMS OF MAJOR DEPRESSIVE DISORDER (S-MDD) SCALE: A NEW PATIENT-REPORTED OUTCOME (PRO) MEASURE DEVELOPED USING A CONSORTIUM-BASED APPROACH**

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**Objective:** Conduct qualitative interviews leading to a developmental version of a new patient-reported outcome (PRO) measure to assess treatment benefit in major depressive disorder (MDD) clinical trials.

**Methods:** Qualitative interviews were conducted with adult MDD patients in the US who recently experienced a major depressive event. All participants had a Hamilton Depression Rating Scale (HAM-D) total score >18 at screening. Experienced interviewers conducted concept elicitation (CE) and cognitive interview sessions using semi-structured interview guides. All interviews were audio recorded and transcribed. CE interviews elicited spontaneous reports of symptom experiences and used probing to further explore and confirm concepts. The CE interviews were coded for qualitative content analysis using Atlas.ti. Data from the CE interviews were considered alongside a review of existing scales, published literature and clinical expert opinion during an item-generation meeting leading to development of a draft scale. Subsequently, interviews were conducted to evaluate understandability, and structure of

the draft scale, to facilitate further refinement. The measurement development field refers to these as “cognitive interviews” - as does the US FDA’s PRO Guidance. The cognitive interview transcripts were summarized in cognitive report tables. In parallel with the cognitive interviews, a translatability assessment (TA) was conducted to help identify those items that presented potential challenges for translation to other languages and cross cultural adaptation (French, Spanish, German, Chinese, and Russian were evaluated). An ePRO migratability assessment was conducted to ensure the viability of implementing the scale on all available electronic data collection platforms.

**Results:** Forty patients [mean age: 46.2; 67.5% female; 45.0% white (non-Hispanic)] participated in the CE interviews. Mean (SD) HAM-D total score of the participants was 24.4 (4.3). A total of 3022 symptom codes, representing 91 different concepts, were derived from the transcripts. During the item-generation meeting, a 36-item draft version of the Symptoms of Major Depressive Disorder (S-MDD) scale was developed. The TA subsequently identified potential translation issues with 3 of the items. Fifteen patients participated in 3 waves of cognitive interviews, which along with the TA led to the removal of 1 item and modification of 4 others. Further changes to formatting and structure of the items and the scale’s instructions were made based on the ePRO migratability assessment.

**Conclusions:** The S-MDD scale is a 35-item PRO measure intended to measure the signs and symptoms of MDD. The S-MDD scale was developed in accordance with the US FDA’s PRO Guidance and best instrument development practices. Following qualification via the FDA’s Drug Development Tool Qualification Program, the S-MDD will be used as an endpoint in MDD clinical trials to support medical product labeling. Qualitative interviews have provided evidence for content validity. Future quantitative studies will confirm the S-MDD scale’s measurement properties, its factor structure, and provide further evidence for qualification.

#### **Learning Objectives:**

- Learn about the Symptoms of Major Depressive Disorder (S-MDD) scale, a new patient-reported outcome measure developed by the PRO Consortium Depression Working Group.
- Learn about the findings of the qualitative research conducted as part of the development of the S-MDD measure.

#### **Source of Funding:**

Funding for this research was provided by the following PRO Consortium members: AbbVie Inc; Bristol-Myers Squibb Company; Eli Lilly and Company; Forest Laboratories, Inc.; Janssen Global Services, LLC; Pfizer Inc.; Shire plc; and Sunovion Pharmaceuticals, Inc.

Critical Path Institute’s PRO Consortium is supported by grant No. U01FD003865 from the United States Food and Drug Administration and by Science Foundation Arizona under Grant No. SRG 0335-08

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**Objective:** Major depressive disorder (MDD) is a heterogeneous disorder that affects patients with different demographic characteristics, symptom severity, disease course, and treatment history. Successful management of MDD requires effective treatment across various patient populations. Levomilnacipran (1S, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with approximately 2-fold greater potency for reuptake inhibition of norepinephrine than serotonin. Sustained release (SR) levomilnacipran is in late-stage clinical development for the treatment of MDD in adults; the SR formulation was developed for once daily dosing. Data from 5 short-term studies were used to evaluate the efficacy of levomilnacipran SR across patient subgroups.

**Methods:** Data from 2 fixed- (NCT00969709, NCT01377194) and 3 flexible-dose (NCT00969150, NCT01034462, EudraCT: 2006-002404-34) randomized, double-blind, placebo-controlled trials of 8-10 weeks' duration that evaluated levomilnacipran SR 40-120 mg/day were analyzed. Patients were 18-78 years of age and met DSM-IV-TR criteria for MDD. The primary efficacy measure in all studies was Montgomery-Åsberg Depression Rating Scale (MADRS) total score change from baseline to endpoint; analysis was based on the modified Intent-to-Treat (ITT) Population using the mixed-effects model for repeated measures (MMRM) approach. Pooled post hoc analyses examined MADRS change from baseline to Week 8 in patient subgroups including sex, age, and baseline depression severity using the MMRM approach.

**Results:** The pooled ITT Population consisted of all patients who had received  $\geq 1$  dose of study drug and had  $\geq 1$  postbaseline MADRS assessment (levomilnacipran SR=1565; placebo=1032). In primary analyses of the individual studies, least squares mean difference (LSMD) for levomilnacipran SR vs placebo in MADRS change from baseline was significantly greater in 2 fixed-dose (40, 80, and 120 mg/d; 40 and 80 mg/d) studies (-3.1 to -4.9;  $P < .05$ ) and 2 flexible-dose (40-120 mg/d; 75-100 mg/d) studies (-3.1 and -4.2;  $P < .01$ ); the difference was not significant in 1 flexible-dose (40-120 mg/d) study (-1.5;  $P = .249$ ). In pooled analyses of all 5 studies, MADRS change was statistically significant for levomilnacipran SR vs placebo (LSMD [95% CI]) in men (-3.5 [-5.0, -2.0]) and women (-2.3 [-3.4, -1.2];  $P < .001$ ), and younger (18-55 years: -2.5 [-3.6, -1.5];  $P < .001$ ) and older ( $\geq 55$  years: -3.4 [-5.3, -1.4];  $P < .001$ ) patients. MADRS change was also significantly greater for levomilnacipran SR vs placebo in patients with different levels of baseline depression severity (MADRS  $< 35$ : -2.6 [-3.8, -1.5];  $P < .001$ ; MADRS  $\geq 35$ : -2.9 [-4.3, -1.4];  $P < .001$ ).

**Conclusions:** In pooled analyses of 5 placebo-controlled trials, levomilnacipran SR showed consistent efficacy across patient subgroups. The difference in MADRS reduction for levomilnacipran SR vs placebo was in excess of 2 points in every patient subgroup, demonstrating clinically relevant improvement across different patient populations.

#### **Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the efficacy of levomilnacipran SR in the treatment of major depressive disorder in men and women, and younger and older patients.
- At the conclusion of this session, the participant should be able to discuss the efficacy of levomilnacipran SR in the treatment of major depressive disorder across different levels of baseline symptom severity.

**Source of Funding:** This analysis was funded by Forest Laboratories.

#### **Literature References:**

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## **EFFECT OF SEROTONERGIC ANTIDEPRESSANT ON ENDOGENOUS BRAIN SEROTONIN IN MAJOR DEPRESSIVE DISORDER AND TREATMENT RESPONSE**

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Research Proposal

**Purpose:** Major depressive disorder (MDD) is projected to be the number one cause of disease burden worldwide in 2030. Selective serotonin reuptake inhibitors (SSRI) are the most commonly prescribed antidepressants however there is a substantial variability in treatment response (Rush et al 2006). In addition, the antidepressant effects of SSRI treatment take several weeks or months for full recovery, and are thought to involve multiple downstream molecular and cellular transcriptional changes, that may impact on the 5-HT system. Investigations to date have relied on indirect measures of 5-HT transmission and therefore the critical question that has still not directly been tested in humans is whether continued SSRI treatment increases 5-HT levels and how this relates to improvement in the symptoms of depression. In a recently completed study, using Positron Emission Tomography (PET) imaging with [11C]CUMI-101, a novel and highly selective 5-HT<sub>1A</sub> PET tracer, I have shown that acute citalopram (an SSRI) infusion induced about a 7% (Cohen's d: 0.97) increase in ligand binding in cortex in healthy human subjects (Selvaraj et al 2012). This likely reflects a raphe 5-HT<sub>1A</sub> autoreceptor-induced reduction in 5-HT release from 5-HT nerve terminals in line with the preclinical evidence (Romero and Artigas 1997). This result indicates that [11C]CUMI-101 is a suitable PET tracer to study endogenous 5-HT changes and physiological function. This observation is also recently been supported by a PET study using a 5-HT<sub>1B</sub> tracer (Nord et al 2013).

**Methodology:** 1) To determine the brain serotonin response to citalopram challenge in MDD patients to directly test the serotonin hypothesis of MDD.

Thirty two unmedicated acutely ill MDD male patients aged 18-60 will receive two [11C]CUMI-101 scans; one with placebo (saline) and followed by another scan after intravenous citalopram 10 mg on the same day. Serum citalopram levels, prolactin levels, BDNF levels will also be measured as the latter has been shown to be a marker of antidepressant response (Sen et al 2008). All participants will be administered a structured clinical interview to confirm diagnosis, as well as the Montgomery-Asberg rating scale, Beck Depression Inventory (BDI), and HRSD17 to index severity.

I predict that unmedicated MDD patients will show increased cortical [11C]CUMI-101 response to citalopram challenge compared to healthy controls in line with the 5-HT hypothesis that cortical serotonin levels are reduced.

2) To determine the effect of continued SSRI treatment on 5-HT functioning.

A repeat citalopram challenge [11C]CUMI-101 scans and all clinical measures will be carried out at the end of 8 weeks of SSRI treatment. Based on PET displacement model, if the SSRI treatment increases 5-HT functioning, I predict that the cortical [11C]CUMI-101 binding will be reduced compared to pre-treatment baseline in MDD patients who responded to treatment. Therefore the serotonin levels increased in frontal cortex. Twelve healthy volunteers will have repeat [11C]CUMI-101 scan for test-retest comparison to control for any effects of time on [11C]CUMI-101 binding.

**Importance:** The proposed experimental paradigm has the potential to be the first in vivo means of assessing changes in brain serotonin levels in MDD patients and is important to understand both the role of 5-HT in MDD and in treatment response.

**Learning Objectives:**

- To understand the antidepressant mechanism in depression
- To understand if the PET imaging measure of serotonin neurotransmission is useful as a treatment response marker

**Source of Funding:** Dr Selvaraj has received lecturer start-up grant from Academy of medical sciences, UK.

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**DISTINCT WHITE MATTER ALTERATIONS ARE ASSOCIATED WITH MAJOR DEPRESSION AND ANHEDONIA SEVERITY IN ADOLESCENTS**

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**Background:** Anhedonia, which reflects deficits of positive valence systems (PVS), manifests a wide severity range among adolescents with major depression (MDD).<sup>1</sup> However, to date, most reward-based investigations have not accounted for anhedonia severity. Here, we examined white matter (WM) integrity in MDD adolescents and controls while relating WM measures to anhedonia severity.

**Methods:** Seventeen MDD adolescents [anhedonia range: 2 - 10, Mean: 5.76 (SD 2.3)] and 16 matched controls, underwent diffusion tensor imaging scans. Maps of fractional anisotropy (FA, WM integrity), mean diffusivity (MD) and radial diffusivity (RD) were generated using tract-based spatial statistics. Significant levels of  $p < 0.001$  and 0.005 were required respectively for group comparisons and correlations within the MDD group.

**Results:** MDD adolescents manifested increased FA along the uncinate fasciculus and decreased MD in the dorsolateral prefrontal cortex. Anhedonia severity was associated with increased WM integrity of the perigenual (pg) anterior cingulate cortex (ACC) and increased RD (decreased WM integrity) of the subgenual (sg) ACC.

**Conclusions:** These findings add to the mounting literature implicating the ACC in PVS deficits.<sup>2</sup> The opposite findings within the pg- and sg-ACC in relation to anhedonia suggest that these key regions underlie distinct reward processes or compensate for each other's dysfunction.

**Learning Objectives:**

- To understand the alterations in WM integrity associated with adolescent MDD.
- To understand the relationship between specific alterations in WM integrity and anhedonia severity.

**Source of Funding:** NIH (AT002395, AT004576, MH077072, MH077072-03S1, MH095807), Chrissy Rossi National Alliance for Research on Schizophrenia and Depression Award, Hope for Depression and Research Foundation

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## DOSE RESPONSE ANALYSIS OF LISDEXAMFETAMINE DIMESYLATE FOR TREATMENT OF BINGE EATING DISORDER

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**Objective:** There are no approved pharmacotherapies for binge eating disorder (BED). Previous drug trials have used single- or flexible-dose designs precluding examination of dose effects. We report dose response of lisdexamfetamine dimesylate (LDX) to treat moderate to severe BED using a pre-specified exploratory analysis with a test for dose linearity. We also report a post hoc analysis using MCP-Mod, a method combining multiple comparisons procedure and dose-effect modeling, to estimate dose response profile and minimum effective dose (MED).

**Methods:** In the context of an 11-wk randomized, double-blind, forced-dose titration trial of efficacy and safety of placebo or LDX (30, 50, or 70mg/d) for treatment of adults with BED significant differences compared to placebo were found with LDX 50 and 70mg/d ( $P<.001$ ) but not 30mg/d ( $P=.35$ ) in the primary measure of mean change from baseline in log-transformed binge days/wk. To assess a potential dose response relationship, a preplanned exploratory analysis of dose response used the full analysis set for log-transformed binge days/wk, using an ANCOVA model and last observation carried forward. The post hoc analysis was performed for change from baseline at wk 11 in un-transformed binge days/wk of study completers only, using MCP-Mod. This sequential, 2-step analysis evaluated a set of pre-specified dose-response profiles to assess best-fit profile and subsequently determine MED. The MED is defined as the lowest LDX dose providing profile-based statistical separation with a clinically meaningful difference (CMD) from placebo in change from baseline to week 11 in un-transformed binge days/wk.

**Results:** Of 266 participants (placebo, n=65; LDX: 30mg/d, n=68; 50mg/d, n=67; 70mg/d, n=66), the preplanned analysis showed that number of binge days/wk decreased with increasing LDX dose and supported a linear dose response. The MCP-Mod analyses assessed linear, logistic, exponential, quadratic, and emax dose-profile models for 213 completers (placebo, n=50; LDX: 30mg/d, n=53; 50mg/d, n=55; 70mg/d, n=55), determining the linear model to be the best fit. The weighted average MED from fitting the data to each curve was 34.0 mg/d, confirming that the 30 mg dose was not effective.

**Conclusion:** LDX treatment improved binge eating behavior in adults with moderate to severe BED. A pre-planned analysis supports a linear dose response. A post hoc analysis, using the MCP-Mod method, supports the linear dose response relationship as the best fit model, as compared to quadratic, emax, exponential, and logistic. The analysis results of weighted average MED being 34.0 mg/d also supports the premise that the 30mg/d fell below the MED criteria.

Clinical research was funded by the sponsor, Shire Development LLC.

### Learning Objectives:

- Understand the dose-response relationship of effects of lisdexamfetamine dimesylate (LDX) vs placebo on the change in binge eating days using best-fit model in adults with binge eating disorder (BED).
- Understand the minimum effective dose of LDX for treatment of BED

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## EFFICACY OF LISDEXAMFETAMINE IN A RAT MODEL OF BINGE-EATING DISORDER

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**Background:** Binge-eating disorder (BED) is a psychiatric condition characterised by episodes of compulsive, excessive consumption of palatable foods, often accompanied by intense anxiety and guilt. Lisdexamfetamine dimesylate ([LDX] Vyvanse®, Venvanse®), a prodrug metabolised to d-amphetamine (d-AMF) by red blood cells (Pennick 2010, Neuropsychiatr Dis Treat 6:317), is approved to treat ADHD. LDX is undergoing clinical evaluation in BED.

**Methods:** We have compared the acute effects of LDX in a rat model of BED and compared it against its active metabolite, d-AMF, and sibutramine (SIB), which is reported to be effective in BED in clinical trials. Forty-four, lean, female, Wistar rats were singly housed on reversed-phase lighting with free access to standard chow. A pot containing ground chocolate was placed in each cage for a 2h period at irregular intervals to establish binge-eating. LDX, d-AMF and SIB were tested after oral administration.

**Results:** After ~4 weeks of irregular, limited access to chocolate reproducible bingeing was established, but rats did not exhibit increased bodyweight compared with controls maintained exclusively on standard chow. LDX (0.1-1.5 mg/kg [d-AMF base]) dose-dependently reduced chocolate bingeing by 13.9%-86.1%. LDX (0.3 mg/kg [d-AMF base]) reduced chocolate bingeing by 40.2% ( $p<0.001$ ) whilst having no effect on standard chow consumption. LDX did not decrease bodyweight. d-AMF (0.1-1.0 mg/kg [d-AMF base]) decreased chocolate bingeing by 0.1%-55.9% with significant reductions at the two highest doses. d-AMF did not reduce standard chow consumption, but did reduce bodyweight at the highest dose. Although SIB (0.3-5.0 mg/kg) attenuated chocolate bingeing, there were similar reductions in chow consumption in the 2hr binge-eating sessions. SIB produced small bodyweight decreases. SIB, but not LDX or d-AMF significantly reduced water intake.

**Conclusions:** The results demonstrate that rats given irregular, limited access to chocolate develop robust, intermittent hyperphagia that is analogous to BED without obesity. Bingeing was markedly attenuated by acute administration of LDX or its metabolite, d-AMF. Both compounds appear advantaged over sibutramine by the fact that they have the potential to control chocolate binge-eating without adversely reducing the consumption of normal food. The data provide evidence to support use of LDX in managing BED in humans.

#### **Learning Objectives:**

- Understand that binge eating behavior in rats is reduced by lisdexamfetamine and by d-amphetamine without decreasing intake of regular chow or water.
- Understand sibutramine reduces binge behavior in rats while also reducing regular chow consumption and significantly reducing water intake.

**Source of Funding:** The preclinical research was supported by Shire Pharmaceuticals Ltd.

#### **Literature References:**

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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.

#### **Learning Objectives:**

- Teachers will be aware of the contents of the 7th edition of the ASCP Model Psychopharmacology Curriculum for Training Directors and Teachers of Psychopharmacology in Psychiatric Residency Programs.
- Teachers will be aware of the contents of the 2nd edition of the ASCP Model Psychopharmacology Curriculum for Directors of Medical Student Education and Teachers of Psychopharmacology in Medical Student Programs.

**Source of Funding:** N/A

#### **Literature References:**

- (2012). ASCP Model Psychopharmacology Curriculum for Training Directors and Teachers of Psychopharmacology in Psychiatric Residency Programs (7th ed.). Retrieved from <http://psychopharmacurriculum.com>
- (2013). ASCP Model Psychopharmacology Curriculum for Directors of Medical Student Education and Teachers of Psychopharmacology in Medical Student Programs. (2nd ed.). Retrieved from <http://psychopharmacurriculum.com>

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### **ELEVATION OF MONOAMINE OXIDASE A IN BORDERLINE PERSONALITY DISORDER WITH HIGH SUICIDAL IDEATION: AN [11C] HARMINE POSITRON EMISSION TOMOGRAPHY STUDY**

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**Introduction:** Borderline personality disorder (BPD) is a common yet serious psychiatric illness characterized by a high suicide risk. Intermittent, severe dysphoric mood states in BPD often precede suicidal behavior. Monoamine oxidase-A (MAO-A) is a pro-apoptotic, oxidative enzyme that degrades mood-regulating neurotransmitters such as serotonin, norepinephrine, and dopamine. MAO-A binding is increased in other dysphoric mood states. We hypothesized that MAO-A binding would be increased in BPD.

**Methods:** We scanned 22 female participants with BPD and 14 age- and sex-matched healthy, control subjects using [<sup>11</sup>C] harmine PET to measure MAO-A V<sub>T</sub> as an index of MAO-A binding. Thirteen BPD patients evidenced moderate dysphoria (HDRS ≤ 24) and nine severe dysphoria (HDRS > 24). Sixteen BPD participants were medication-free; six were taking a psychotropic medication. All participants were non-smokers and free of illicit substance use. MAO-A V<sub>T</sub> was measured in prefrontal cortex (PFC), anterior cingulate cortex (ACC), anterior temporal cortex, caudate, putamen, thalamus, hippocampus, and midbrain.

**Results:** MAO-A  $V_T$  was elevated in BPD versus healthy participants in PFC and ACC ( $F_{2,33} = 14.6$ ,  $p < .001$ ; elevated 36% and 32% in PFC and ACC, respectively). PFC and ACC MAO-A  $V_T$  were found to be 52% and 48% greater, respectively, in BPD with severe dysphoria compared to health. BPD participants with severe dysphoria reported greater suicidal ideation than BPD subjects with moderate severity; suicidality was positively correlated with PFC MAO-A  $V_T$  (Spearman's  $\rho = 0.61$ ,  $p < .01$ ).

**Conclusions:** This is the first study to show elevated MAO-A in BPD. The magnitude of MAO-A increase in BPD is the largest observed to date in a psychiatric condition. Our findings suggest that novel therapeutics combining MAO-A inhibition with monoamine reuptake inhibitors could be beneficial in treating BPD with severe dysphoria and suicidality.

**Learning Objectives:**

- To describe the hypothesized role of monoamine oxidase A in dysphoric mood states, including borderline personality disorder
- To understand how novel therapeutics combining monoamine oxidase A inhibition with monoamine reuptake inhibitors could prove helpful in treating symptoms of BPD, including suicidality

**Source of Funding:** Physicians' Services Incorporated Foundation

**Literature References:**

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**PATIENT FUNCTIONING AND MEDICATION SATISFACTION WITH PALIPERIDONE PALMITATE FOLLOWING TREATMENT OF ACUTE EXACERBATION OF SCHIZOAFFECTIVE DISORDER**

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**Introduction:** This analysis examined functioning using the PSP scale and medication satisfaction using the MSQ scale during the 25-week open-label (OL) phase of a maintenance study in schizoaffective disorder (SCA) (randomized, double-blind [DB], placebo-controlled international study of the long-acting injectable antipsychotic paliperidone palmitate [PP]).

**Method:** Investigators analyzed OL data from an ongoing, multiphase study in patients with acute exacerbation of SCID-confirmed SCA (NCT01193153). Subjects stabilized on PP (78–234 mg/mo) during a 13-week OL flexible-dose period continued into a 12-week OL fixed-dose period. Those maintaining stability in this OL phase were randomized to PP or placebo in a 15-month DB phase. Assessments included PSP, patient-rated MSQ, and overall clinical status via CGI-S-SCA. PSP is scored 1–100 (higher score indicates better functioning) based on evaluation of four domains (socially useful activities, personal and social relations, self-care, disturbing/aggressive behaviors); the level of function for each PSP domain is assessed on a 6-point severity scale: absent, mild, manifest, marked, severe, very severe. MSQ is a 7-point scale: 1=extremely dissatisfied; 7=extremely satisfied. CGI-S-SCA is scored 1–7 (normal to most severely ill). Data from the OL phase included all subjects who had at least one injection. Mean changes from baseline to OL LOCF end point were examined using paired *t*-test.

**Results:** 667 subjects enrolled; 349 completed the OL phase. Mean (SD) age: 39.5 (10.7) years; 54% male; 49% on PP monotherapy, 51% on adjunctive antidepressants (AD) or mood stabilizers (MS). Mean (SD) baseline PSP and CGI-S-SCA scores: 51.6 (10.9) and 4.4 (0.6), respectively. Mean (SD) PSP score improvement at end point: 13.6 (14.9) ( $P < 0.001$ ). Mean (SD) change at end point in CGI-S-SCA score: -

1.3 (1.1) ( $P<0.001$ ). Subjects with manifest to very severe impairment on PSP domains of socially useful activities and personal and social relations decreased from 92.2% and 89.1% at baseline to 58.6% and 46.0% at end point. Subjects with manifest to very severe impairment on PSP domains of self-care and disturbing/aggressive behaviors decreased from 28.9% and 36.7% at baseline to 11.9% and 9.9% at end point. Proportion of subjects “satisfied” with their medication per MSQ score (5–7) increased from 38.2% at baseline to 75.1% at end point.

**Conclusion:** Results suggest that functioning and medication satisfaction improved in tandem with symptom improvement during 25 weeks following treatment with PP as monotherapy or adjunctive to MS/AD in acutely ill subjects with SCA.

**Learning Objectives:**

- To educate participants on characteristics of schizoaffective disorder
- To determine the role of paliperidone palmitate in functioning and in medication satisfaction of acutely ill patients with schizoaffective disorder

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

**Literature References:**

- Canuso CM, Turkoz I, Fu DJ, Bossie CA. Role of paliperidone extended-release in treatment of schizoaffective disorder. *Neuropsychiatr Dis Treat*. 2010;6:667-679
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**PRE-DIABETIC PATIENTS IN A DIET/EXERCISE PROGRAM: THE USE OF METFORMIN WITH REGARDS TO TRENDS IN PSYCHIATRIC ILLNESS**

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**Purpose:** To determine the effects of metformin use upon the mental health status of pre-diabetic individuals with a history of enrollment in a diet/exercise program.

**Background:** The link between diabetes and mental illness has been surveyed in the past with a higher prevalence of the latter demonstrated. It is thought that by ensuring more appropriate glucose management through the employment of diet, exercise, and medication therapy, the onset of mental health conditions may be delayed. Various studies have shown the impacts of oral anti-diabetic agents, such as metformin, in assisting with diabetes control. This medication may lower basal and postprandial glucose levels by reducing intestinal glucose absorption and hepatic gluconeogenesis, as well as by increasing peripheral glucose utilization. The impacts have yet to be clearly demonstrated from a mental health perspective amongst the pre-diabetic population so that earlier benefits of medication use coupled with lifestyle measures may potentially be gleaned.

**Methodology:** This pilot project involved a retrospective comparison between individuals enrolled in a diet/exercise program with a history of metformin use for greater than or equal to 3 months to those individuals without such a history of medication use while being enrolled in a diet/exercise program. Individuals with a history of mental illness (depression, anxiety disorder, bipolar, schizophrenia, substance use disorder, etc.) were further compared between groups for Charlson Co-morbidity Score, concomitant medication use, and socioeconomic status differences.

**Results:** Out of 29 pre-diabetic individuals enrolled in a diet/exercise program with metformin use, 4 were diagnosed with psychiatric illnesses post-exposure, out of which 3 had a Charlson Co-morbidity score  $\geq 1$ , a medication burden of  $\geq 9$  concomitant therapies, and were of lower socioeconomic status (household income  $< \$40,000$  per year). Out of 11 pre-diabetic individuals enrolled in a diet/exercise program without metformin therapy, 8 were diagnosed with psychiatric illnesses, out of which 3 had a Charlson Co-morbidity score  $\geq 1$ , 8 had a medication burden of  $\geq 9$  concomitant therapies, and 3 were of lower socioeconomic status. All individuals analyzed were similar with respect to family history of mental illness.

**Importance:** Mental illness was found to be more closely associated with lack of metformin use alongside diet/exercise therapy amongst project participants with potential effects shown from differences in baseline parameters. Further studies are needed in the field to more fully ascertain and address this concern.

**Learning Objectives:**

- To demonstrate the role of metformin in treating pre-diabetes with potential impacts upon mental health status.
- To identify patterns in co-morbidity index, medication burden, and socioeconomic status amongst study participants.

**Source of Funding:** N/A

**Literature References:**

- Florez H, et al. Impact of lifestyle intervention and metformin on health-related quality of life. *J Gen Intern Med* 2012 Dec; 27: 1594-601.
- Meyer JM and Stahl SM. The metabolic syndrome and schizophrenia. *Acta Psychiatr Scand* 2009 Jan; 119: 4-14.

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**EXTERNAL TRIGEMINAL NERVE STIMULATION: ADJUNCTIVE NEUROMODULATION FOR COMORBID POST-TRAUMATIC STRESS DISORDER AND MAJOR DEPRESSION**

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**Purpose and Content:** Modulation of brain activity via external stimulation of the Trigeminal Nerve (eTNS) is an emerging therapy for epilepsy and depression, with an excellent safety profile and significant improvements in seizures and mood in preliminary studies in subjects with treatment-refractory illnesses. The Trigeminal nerve has reciprocal projections to the nucleus tractus solitarius, the locus coeruleus, the raphe nuclei, and the reticular formation, suggesting eTNS may be able to alter activity in structures implicated in mood regulation and anxiety disorders. In this proof-of-concept project, the effects of eTNS were examined in Post-traumatic Stress Disorder (PTSD) with comorbid unipolar Major Depressive Disorder (MDD) as an adjunct to pharmacotherapy.

**Methods:** Twelve adults with PTSD and MDD were studied in an 8-week open outpatient trial (age 52.8 (13.7 sd), 8F:4M, median 37 years since trauma; ATHF at least 1). Subjects stimulated the supraorbital branches of the trigeminal for 8 hours each night, as changes in the PTSD Patient Checklist (PCL) and Quick Inventory of Depressive Symptomatology (QIDS-C) were monitored at each visit, and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) was completed at the intake and final visits.

**Results:** Decreases in PCL score were significant, from 63.3 (7.8) at entry to 43.0 (18.3) at week 8 (2-tail paired t-test  $p=0.003$ ). QIDS-C score decreases were also significant, falling from 17.8 (4.0) to 8.8 (4.3) ( $p < 0.001$ ). All reflect a large effect size comparing end-of-trial to start (Cohen's  $d$  1.5 for PCL, 1.8 for QIDS-C). Q-LES-Q scores showed significant improvement in quality of life ( $p<0.002$ ).

**Conclusions:** Significant improvements in PTSD and depression severity were achieved in the 8 weeks of acute eTNS treatment, along with effects on quality of life. This novel approach to brain stimulation may have use as an adjunct to pharmacotherapy in these disorders if efficacy and tolerability are confirmed with additional studies.

**Learning Objectives:**

- describe recent and current research into trigeminal nerve stimulation as a therapeutic intervention in neurological and psychiatric disorders
- critically consider the next research steps needed to evaluate this adjunctive form of neuromodulation

**Source of Funding:** NeuroSigma, Inc. (investigator initiated trial)

**Literature References:**

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## **IMPLEMENTATION OF AN INNOVATIVE TOOL FOR TRACKING CHANGES IN PRESCRIBED MEDICATION IN COMPARATIVE EFFECTIVENESS RESEARCH: LESSONS LEARNED**

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**Objective:** Treatment of Bipolar Disorder (BD), as with many psychiatric illnesses, involves complex medication regimens that rarely remain fixed<sup>1</sup>. Although there are standardized treatment algorithms for BD<sup>2</sup>, physicians often deviate from guidelines to personalize treatment. In comparative effectiveness research (CER) for complex disorders, clinicians will frequently change adjunctive medications. The Medication Recommendation Tracking Form (MRTF) was developed as a tool for use in CER to track physician prescribing behavior. We will discuss the challenges and successes of implementing this novel tool in a research study.

**Methods:** The MRTF was developed for the NIMH LiTMUS Study (N=283)<sup>3</sup> and further refined for use in the AHRQ-funded Bipolar CHOICE study, a nationwide multi-site comparative effectiveness trial comparing lithium and quetiapine over 6 months of treatment (N=484). Our goal was to track physician prescribing behavior throughout the study across sites. In CHOICE, study physicians were trained on the MRTF at a start-up meeting and compliance was assessed through conference calls, site monitoring visits, and data reports. We also examined the distribution of the types of medication changes as a measure of physician prescribing behavior.

**Results:** Overall, physicians were able to learn how to correctly and effectively use the MRTF quickly. It was important to ensure that all sites were using the form in the same, standardized way. The most difficult aspects for physicians to grasp were using the correct reason for change (e.g. specifying “Planned Dose Titration” rather than “Side Effects” if the change in dose was part of the original treatment plan), and only recording their recommendations rather than actual patient behavior. Data reports gave detailed information about how physicians were using the form and helped to inform how site monitors should re-train clinicians. The MRTF provided a clear breakdown of the reasons for change used at each visit in the LiTMUS study, with “Planned Dose Titration” and “Symptoms” being the most common.

**Conclusions:** The MRTF is an innovative and useful tool for tracking changes in medication in CER because it requires physicians to list their recommended changes and reasons for doing so. The strategy for successful implementation of a new measure begins with a well-developed form with as many predetermined options as possible, and includes frequent and clear communication between physicians, research assistants, and site monitors, and regular monitoring with detailed data reports.

### **Learning Objectives:**

- A novel tool that tracks physician prescribing behavior
- Effectively implementing a new measure

**Source of Funding:** NIMH N01MH8001, AHRQ 1R01HS019371-01

**Literature References:**

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- Suppes, T., et al. The Texas Implementation of Medication Algorithms: Update to the algorithms for treatment of bipolar I disorder. *Journal of Clinical Psychiatry* 2005; 66(7): 870-86.
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**THE ROLE OF THE PHARMACIST RESEARCHER ON AN INTERDISCIPLINARY CORRECTIONAL MENTAL HEALTH RESEARCH TEAM**

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Poor health conditions are exacerbated by lifestyle, and for many poor, uneducated, and unemployed individuals, they find themselves involved with criminal justice systems and incarcerated. Health conditions that remained unaddressed prior to incarceration now challenge corrections facilities, which only more recently (*Estelle v Gamble*), have been mandated to provide a standard of care that approximates a community standard of care. Although questions exist about whether health care behind bars could improve the health status of our communities, the reality exists that nearly 95 % of persons living in prisons will be released (*Satcher, 2007*). With the majority of inmates eventually released back to their communities, there is a tremendous public health opportunity to benefit the community with reduced illness rates, financial savings, improved public safety, and better use of existing health care system resources (*Travis, Solomon & Waul, 2001*). Acknowledging that what happens to the health of inmates and ex-inmates impacts the health of the public acknowledges correctional healthcare as an important component of public health care.

Pharmacists are an essential component of the healthcare system, essential for managing the acquisition of medication histories, monitoring and managing medication use in collaboration with other members of the health-care team, and providing medication information for both community and hospitalized patients treated with complex and high-risk medication regimens. Pharmacists also play a vital role in the therapeutic alliance to improve medication adherence.

The purpose of this poster is to describe the Correctional Health Research Team at the University of Connecticut and the various roles a pharmacist has performed as a team member, including several research projects. These projects include determination of medication adherence in a bipolar disorder population, development of an inmate interview for medication adherence, and determination of the prevalence of metabolic syndrome in the correctional setting. Through these projects, the pharmacist has become an essential player in the implementation of an interdisciplinary treatment team within the Correctional setting.

**Learning Objectives:**

- To describe the current state of health care in the Correctional Setting.
- To describe the role of a pharmacist in the development and implementation of a Interdisciplinary Correctional Mental Health Research Team.

**Source of Funding:** University of Connecticut Cross Campus Internal Grant

**Literature References:**

- Satcher D. Ethnic disparities in health: the public's role in working for equality. *PLoS Med* 2006;3(10):e405.
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## **FAILED TRIALS AND PROTOCOL DESIGN: IS THERE A RELATIONSHIP?**

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As the concern over late phase trial failure and high placebo response rates continues, the research industry has voiced a concern that protocol designs are contributing to this pressing issue. In 2007, the Tufts Center for the Study of Drug Development heard the concerns from sponsors, CROs, and investigator sites that protocol designs had become more difficult, more time consuming and with more narrow subject targets and was concerned over the relationship of these factors. A data analysis was conducted on 10,038 protocols which verified that protocol designs have become more demanding, and this may have had a negative impact on trial performance. Their recommendation was to simplifying protocol designs, which should improve trial speed and efficiency substantially.

This poster is designed to outline our review of five years of clinical trials for depression utilizing antidepressants as the IP to see if a correlation exists between protocol design and study outcome. Both centers reviewed all protocols that had been operationalized. They evaluated protocol design, including length of screening visit, numbers of procedures during follow-up visits, number of primary efficiency measures being performed by the Investigator vs. the study coordinator vs. outside vendor, and number of inclusion and exclusion elements in contrast to successful outcomes, including drug separation and placebo rate.

The results show that feedback to the sponsors and protocol designers regarding the increase in patient questionnaires, subjective assessments, number of inclusion and exclusion criteria, and delegation of primary efficacy ratings, along with other unique procedures, is needed in order to ensure the best possible outcomes.

### **Learning Objectives:**

- Be able to outline the changes in protocol design over the last 5 years and their impact on sites' burden for implementation
- Be able to outline the effect of protocol design changes over the last 5 years and their effect on study outcome experience for two sites

**Source of Funding:** No funding source

### **Literature References:**

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## **CHARACTERISTICS OF DUPLICATE SUBJECTS IN A CLINICAL TRIAL SUBJECT REGISTRY**

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**Background:** Duplicate and professional subjects are a growing problem in CNS clinical trials and are not easily characterized on the basis of age, gender, race or socioeconomic status.

**Methods:** Subject authorized partial identifiers of prescreening CNS subjects presenting at participating Southern California sites were entered into the CTSdatabase subject registry. All subjects and the subset of subjects who matched with subjects entered at other sites were stratified by gender and age into 10-year cohorts. These cohorts were compared with each other and with cohort data from the 2010 US Census.

**Results:** 47.8% of all subjects entered and 45.8% of all duplicates were female. Few subjects under 20 or over 70 years old were entered into the registry.

57.9% of all subjects entered in the registry and 53.7% of all duplicate subjects were between the ages of 40 and 59. The most *common* duplicate subject in this sample, over a quarter of all duplicates, was a male in his 40's.

The *likelihood* of an individual member of an age-gender cohort being a duplicate, however, did not vary significantly across cohorts.

**Conclusion:** While 40-59 year olds were the most common group to be prescreened *and* to be duplicates in this sample, all ages and genders were represented among the duplicates. Men and women in all age groups, and particularly middle aged men in this sample, contribute to the problem of dual enrollment. Age and gender alone cannot predict which subjects are more likely to seek to enroll in multiple studies.

**Learning Objectives:**

- Participants will identify gender and age characteristics of prescreen subjects entered in a clinical trial subject registry.
- Participants will be able to identify demographic characteristics of duplicate prescreens entered into a subject registry.

**Source of Funding:** N/A

**Literature References:**

- Brody B, Leon AC, Kocsis, JH Antidepressant Clinical Trials and Subject Recruitment: Just Who Are Symptomatic Volunteers? *AmJPsychiatry* 168:12,1245-1247, December 2011
- Clinical Trial Facts and Figures. (1/9/13) Retrieved from [http://www.ciscrp.org/professional/facts\\_pat.html](http://www.ciscrp.org/professional/facts_pat.html)

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**EFFECTS OF LEVOMILNACIPRAN SR ON MEASURES OF ATTENTION IN A PHASE 3 TRIAL OF MAJOR DEPRESSIVE DISORDER (MDD)**

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**Background:** Attention is compromised in MDD, but the relationship of attention deficits to depression symptom severity is unclear. Levomilnacipran SR (LVM; 1S, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor in late-stage clinical development for MDD. LVM has 2-fold greater potency for norepinephrine relative to serotonin reuptake inhibition and over 10-fold higher selectivity for norepinephrine reuptake inhibition compared with duloxetine or venlafaxine; the sustained release (SR) formulation allows once-daily dosing.

**Objectives:** To evaluate the improvement in measures of attention following treatment with LVM, and the extent to which such changes are related to changes in measures of depression symptoms.

**Methods:** Patients were randomized (1:1) to levomilnacipran SR (LVM) 40-120 mg/day or placebo (PBO) in an 8-week double-blind study (NCT00969709) of MDD patients with Montgomery-Asberg Depression Rating Scale, Clinician Rated (MADRS-CR)  $\geq 30$  and MADRS-Self Rated (MADRS-SR)  $\geq 26$ . Cognitive assessments included the Cognitive Drug Research System for Attention (Wesnes et al, 2000). The tests included 3 computerized tasks (The Simple Reaction Time, Digit Vigilance, and Choice Reaction Time). Parallel forms of each task were used to allow for repeated assessment by presenting different, but equivalent, stimuli at each administration. Speed and accuracy measured from the tasks were used to derive 4 composite scores (*power of attention (PoA)*, *continuity of attention (CoA)*, *cognitive reaction time (CRT)*, and *reaction time variability (RTV)*), as well as *digit vigilance task accuracy (DV%)*. Post hoc analyses were conducted using ANCOVA models with treatment group and site as factors (and responder, responder-by-treatment for responder-related analyses) and baseline value as covariates; last observation carried forward (LOCF) approach was used for missing values. Logistic regression was used for MADRS response rates.

**Results:** Change from pre-dosing data were available at 8 weeks for 187 placebo patients and 182 LVM patients. Improvements to attention with LVM over placebo occurred on CoA ( $p=.0036$ ), PoA ( $p=.0666$ ),



RTV ( $p=.0600$ ), CRT ( $p=.296$ ) and DV% ( $p=.0253$ ); similar results were obtained excluding site as a factor in the ANCOVA model. The response rates (MADRS reduction  $\geq 50\%$  from baseline) were 41.9% for LVM and 29.4% with placebo ( $p=.0083$ ). For DV%, LVM-treated MADRS responders improved by 3.1 DV% units ( $p=.020$ ), compared with declines in other groups: -1.5 unit in placebo-treated responders ( $p=.32$ ), -0.8 in LVM-treated non-responders ( $p=.52$ ), and -1.8 in placebo-treated non-responders ( $p=.094$ ).

**Conclusions:** Improvement in attention deficits in MDD patients were observed following LVM treatment relative to placebo treatment. The observed change could be the result a direct action upon brain structures that control attention, as opposed to a secondary effect of reducing the symptoms of depression.

**Learning Objectives:**

- To understand the effects of levomilnacipran on various measures of cognition
- To understand the effects of levomilnacipran on cognitive measures among patients classified as MADRS responders or nonresponders

**Source of Funding:** The clinical trial was funded by Forest Laboratories, Inc.; analyses were performed by Bracket and Forest.

**Literature References:**

- Wesnes KA, et al. The memory enhancing effects of a ginkgo biloba/panax ginseng combination in healthy middle-aged volunteers. *Psychopharmacology (Berl)* 2000;152(4):353-61.
- Sambunaris A, Bose A, Gommoll C, Chen C, Greenberg WM, Zukin SR, Sheehan DV: W14. A Phase III, Double-Blind, Placebo-Controlled, Flexible-Dose Study of Levomilnacipran SR in Patients with Major Depressive Disorder. *Neuropsychopharmacol.* 2012;38(suppl 1):S322-323.

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## **THE APPLICATION OF COGNITIVE NEUROSCIENCE TO CLINICAL RESEARCH III: EVIDENCE FROM A COGNITIVE TASK OF COMPROMISED NEUROGENESIS IN SCHIZOPHRENICS**

Keith Wesnes, PhD<sup>1</sup>

<sup>1</sup>Bracket

**Background:** Recent evidence indicates that the G-protein coupled receptor, SREB2/GPR85, a known schizophrenia risk factor, negatively regulates hippocampal dentate gyrus neurogenesis-dependent spatial pattern separation in mice (Chen et al, 2012). Post-mortem evidence of compromised hippocampal dentate gyrus (DG) neurogenesis in schizophrenics has also just appeared (Walton et al, 2012). The CDR System automated picture recognition task yields an object pattern separation (OPS) measure, sensitive to DG activity, which in man selectively declines in aging and mild cognitive impairment; and has recently been found to be impaired in several other conditions in which neurogenesis is disrupted. The object of this study was to determine if DG-sensitive OPS is selectively compromised in schizophrenia.

**Methods:** The CDR System OPS task was administered to 91 stably mediated schizophrenic patients aged 22 to 63 years and the results contrasted to 2,330 age-matched healthy controls. Performance on the OPS task was also assessed according to Clinical Global Impression Severity (CGI-S) scores.

**Results:** 2-factor ANCOVA, with Normal v Schizophrenic as one factor and DG v non-DG OPS measures as the other, yielded a significant interaction between the two factors ( $p=0.0005$ ). The difference in % accuracy scores between the populations in the DG sensitive measure was 12.8 (Effect size 1.01), compared with 5.3 (Effect size 0.42) for the non-DG sensitive measure. No such interaction was seen in a comparable forced choice non-DG differentially sensitive verbal recognition task ( $p=0.57$ ), indicating that the OPS effect was not due to response style on such tasks. Importantly, within the 91 patients, CGI-S was significantly associated with the DG sensitive score ( $p<0.05$ ; CGI-S 2=74%; CGI-S 3=66%; CGI-S 2=49%), but not the non-DG sensitive score ( $p=0.91$ ).

**Conclusions:** This is to our knowledge the first robust cognitive data from an OPS task with established DG sensitivity to show a selective deficit in schizophrenics compared to normals; further supported by statistically reliable disease severity deficits. The implications are that part of the memory deficit in schizophrenia is related to compromised DG neurogenesis and that this deficit may respond to

medications which influence neurogenesis; a mechanism possessed by many second generation antipsychotics including olanzapine, risperidone, paliperidone, aripiprazole and possibly quetiapine. This OPS task can serve as both a proof of principle that a compound has neurogenesis activity while also serving as a measure of efficacy.

#### **Learning Objectives:**

- Appreciate how a cognitive task can reflect neurogenesis activity in the dentate gyrus and act as a noninvasive biomarker
- Learn breaking evidence that a cognitive task can support animal and post-mortem work to identify disease severity related disruption to neurogenesis in schizophrenics.

**Source of Funding:** Bracket, Wayne, PA, USA & CRI Lifetree, Philadelphia, USA

#### **Literature References:**

- Chen Q et al. (2012) SREB2/GPR85, a schizophrenia risk factor, negatively regulates hippocampal adult neurogenesis and neurogenesis dependent learning and memory. *European Journal of Neuroscience* 1-12 doi:10.1111/j.1460-9568.2012.08180.x.
- Walton NM et al (2012). Detection of an immature dentate gyrus feature in human schizophrenia/bipolar patients. *Translational Psychiatry* 2: e135.
- Eriksson PS, Perfilieva E, Björk-Eriksson T et al. (1998) Neurogenesis in the adult human hippocampus. *Nature Medicine* 4: 1313-1317
- Sahay A et al (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472: 466–470.

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### **EFFECTS OF ARIPIPRAZOLE ONCE-MONTHLY VS. PLACEBO ON DOMAINS OF PERSONAL AND SOCIAL PERFORMANCE IN YOUNGER AND OLDER PATIENTS WITH SCHIZOPHRENIA**

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**Objective:** To evaluate if younger patients (≤35 years) showed a different pattern of changes on personal and social performance (PSP) scale line items than older patients (>35 years) receiving aripiprazole once-monthly (ARI-OM) vs. placebo in the treatment of schizophrenia.

**Methods:** This was a 52-week, double-blind, placebo-controlled study assessing the efficacy and safety of ARI-OM vs. placebo. The study had 4 phases: Phase 1: oral conversion, patients were cross-titrated from other antipsychotic(s) to oral aripiprazole; Phase 2: oral stabilization with aripiprazole; Phase 3: ARI-OM stabilization, with co-administration of oral aripiprazole in the first 2 weeks; and Phase 4: randomized, double-blind, placebo-controlled maintenance phase. The PSP scale score is based on each of 4 domain scores in a 6-point scale (0–5; absent to very severe). Severity scores in the 4 domains and clinical judgment determine the total PSP score (10-point intervals; 0–100 scale). Exploratory post-hoc analyses were performed in subpopulations of younger patients (≤35 years) and older patients (>35 years) at endpoint (52 weeks) comparing treatment differences between ARI-OM and placebo in mean change from baseline on PSP Total, and the 4 domain scores within each subpopulation using last observation carried forward (LOCF) and ANCOVA.

**Results:** 403 subjects entered Phase 4 of which 394 had baseline PSP evaluations (younger patients: ARI-OM n=93, placebo n=47; older patients: ARI-OM n=171, placebo n=83). The treatment differences (mean change from baseline at Week 52 [LOCF] for ARI-OM–placebo) showed that younger (5.62;

p=0.01) and older (3.54; p=0.01) patients receiving ARI-OM demonstrated statistically significant differences in favor of ARI-OM versus placebo in PSP Total scores, with a greater treatment difference in younger patients. The treatment differences for the PSP “socially useful activities” domain (younger patients: -0.32, p=0.05; older patients: 0.02, p=non-significant), PSP “personal and social relationships” domain (younger patients: -0.39, p=0.01; older patients: -0.23, p=0.05) and PSP “disturbing and aggressive behaviors” domain (younger patients: -0.44, p=0.01; older patients: -0.26, p=0.001) also showed numerically greater differences in favor of ARI-OM for younger compared with older patients. The treatment differences for the PSP “self-care domain” were -0.12 (p=non-significant) in younger patients and -0.26 (p=0.01) in older patients.

**Conclusion:** Treatment differences on the PSP Total score and three social PSP domains suggest that younger patients ( $\leq 35$  years) with schizophrenia may be more sensitive to preservation of function than older patients ( $> 35$  years) after treatment with ARI-OM. Further prospective studies are warranted to confirm the preliminary results based on post-hoc exploratory analysis.

**Learning Objectives:**

- To understand the impact of long-term stability of medication on personal and social functioning
- To understand the potential benefits of treatment early in the course of illness with regard to preservation of personal and social functioning

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

**Literature References:**

- Kane et al. J Clin Psych 2012;73:617–24
- Morosini et al. Acta Psychiatrica Scand 2000;101:323–9

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**IDENTIFICATION OF THE CAUSAL RELATIONSHIPS BETWEEN NEUROCOGNITION, PSYCHOPATHOLOGY, AND FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA**

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**Background:** Cognitive function, social cognition and negative symptoms have been identified as significant contributors to illness course, community functioning and treatment response. Although, cognitive deficits, social cognition and negative symptoms share many characteristics and may be correlated in their severity, these constructs have not been understood in terms of their relationship amongst each other, how similar these constructs are to each other, and whether they are caused by the same underlying pathophysiological factors. The present study sought to examine the relationship of social cognition, psychopathology symptoms, social functioning and other clinical and demographic variables in patients with schizophrenia.

**Method:** The sample was comprised of patients diagnosed with DSM-IV schizophrenia (N = 78) with  $\geq 5$  years illness duration, a MMSE  $\geq 24$  and a total PANSS score  $\geq 60$ . All patients were recruited as they were admitted to a long term psychiatric rehabilitation program. Neurocognition, social cognition, psychopathology, and psychosocial functioning were measured at baseline with the PANSS, MCCB-MATRICES, Facial Emotion Identification Task (FEIT), the PSP and extrapyramidal symptom scales. A subset of patients (n = 8) also completed tests of Theory of Mind, Attributional Style, and Performance-Based Skills Assessment (UPSA-Brief). The empirical independence of these constructs were tested using confirmatory factor analysis (CFA) and the possible causal structure among neurocognition, social cognition, psychopathology and psychosocial functioning was investigated using latent difference score (LDS) analysis.

**Results:** Most patients (78.21%) scored at least one standard deviation below the average T-Score ( $\leq 50$ ) in all domains of neurocognition and on the MSCEIT. A two-factor model of social cognition (MSCEIT and FEIT) and neurocognition (MCCB domains) fit the data well, demonstrating the empirical independence of social cognition functions from neurocognitive domains. The LDS model support a

causal pattern that suggests that neurocognition underlies social cognition as measured by MSCEIT scores and FEIT scores, and that neurocognition and social cognition are significantly related to personal and social performance as measured by the PSP. Linear regression analysis determined younger age ( $\leq 40$  years), lower scores on the PANSS Marder negative domain score, and shorter chronicity of illness as being significantly associated with lower scores on Attention/Vigilance, Processing Speed and emotion perception.

**Conclusion:** The results, in line with recent literature, show a two-factor model consisting of social cognition and neurocognitive measures underlying the three domains of cognitive, social cognition deficits and negative symptoms. However, our results also point to a significant relationship of cognition and social functioning. Overall, these results suggest that some aspects of social cognition and neurocognition could have independent and distinct causal effects on functional outcomes. These results may also support separate therapeutic interventions for treatment for neurocognition and social cognition deficits in schizophrenia.

**Learning Objectives:**

- This presentation will allow the audience to better understand the relationships between neurocognition, psychopathology, and functional outcomes in schizophrenia
- The poster presentation may also show the separate therapeutic interventions for treatment for neurocognition and social cognition deficits in schizophrenia.

**Source of Funding:** Manhattan Psychiatric Center

**Literature References:**

- Tas C, Brown E, Cubukcuoglu Z, Aydemir O, Danaci AE, Brüne M. Towards an integrative approach to understanding quality of life in schizophrenia: The role of neurocognition, social cognition, and psychopathology. *Compr Psychiatry*. 2012 Sep 18.
- Lysaker PH, Gumley A, Luedtke B, Buck KD, Ringer JM, Olesek K, Kukla M, Leonhardt BL, Popolo R, Dimaggio G. Social cognition and metacognition in schizophrenia: evidence of their independence and linkage with outcomes. *Acta Psychiatr Scand*. 2012 Sep 11.

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**LONG-ACTING INJECTABLE VS. DAILY ORAL ANTIPSYCHOTIC TREATMENT TRIALS IN SCHIZOPHRENIA: DO PRAGMATIC VS. EXPLANATORY STUDY DESIGNS MATTER?**

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**Introduction:** Potential advantages of long-acting injectable (LAI) antipsychotics (APs) over daily oral APs in patients with schizophrenia lie in theoretical advantages associated with removing the need for daily adherence. Published studies on this topic are inconclusive. Non-inferiority trials are unable to address this due to the inherent nature of their design. Traditional efficacy trials cannot easily address questions related to adherence with naturalistic use due to highly controlled/defined conditions that can interfere with important real-world differences. To further explore this, we examined the pragmatic (effectiveness) and explanatory (efficacy) nature of recently published relevant trials and related these to the study outcomes.

**Methods:** A literature search identified direct comparative studies of LAIs vs oral APs in schizophrenia with  $\geq 100$  subjects and excluded non-inferiority-, switch-, or pharmacokinetic-studies, or post hoc analyses. It identified 8 studies: 1) Grimaldi-Bensouda et al 2012; 2) Tiihonen et al 2011; 3) Rosenheck et al 2011; 4) Macfadden et al 2010; 5) Gaebel et al 2010; 6) Olivares et al 2009; 7) Zhu et al 2008; and 8) Tiihonen et al 2006. The studies were rated by abstract author consensus using ASPECT-R (A Study Pragmatic: Explanatory Characterization Tool-Rating), derived from an existing tool (PRECIS) developed to assist researchers in designing trials that are either more pragmatic or more explanatory (Thorpe et al, 2009; Tosh et al, 2011). ASPECT-R consists of revised domains and descriptive anchors for rating study design elements of: participant selection, intervention flexibility-experimental and -comparison, medical practice setting/practitioner expertise-experimental and -comparison, follow-up intensity/duration, primary trial outcomes, and participant compliance. Domains ratings: 0=extremely

explanatory, 1=very explanatory, 2=explanatory, 3=elements of both, 4=pragmatic, 5=very pragmatic, 6=extremely pragmatic.

**Results:** Studies 2, 6, 7: all domains were rated as more pragmatic and all concluded an advantage for LAI vs oral APs. Study 1: most domains were rated as more pragmatic and it concluded an advantage for an LAI vs oral APs. Studies 3 and 5: domains were rated as having both pragmatic/explanatory design elements - Study 3 concluded no advantage for an LAI vs oral APs while Study 5 concluded an advantage. Study 4: most design domains were rated as more explanatory – it concluded no advantage for an LAI vs oral AP.

**Conclusion:** Results suggest that those studies with more pragmatic vs explanatory designs demonstrate advantages for LAI vs oral antipsychotics. Explanatory designs may introduce features that obscure potential differences. Other unidentified factors may influence outcomes. Confirmation by independent raters with ASPECT-R is needed.

#### **Learning Objectives:**

- To rate the pragmatic/explanatory nature of published trials comparing long-acting injectable and daily oral antipsychotics using the tool, ASPECT-R.
- To examine the relationship between the pragmatic/explanatory nature of these trials and their results.

#### **Source of Funding:**

Supported by funding from Janssen Scientific Affairs, LLC.

#### **Literature References:**

- Thorpe KE, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol* 2009; 62:464-475.
- Tosh G, et al. Pragmatic vs explanatory trials: the Pragmascope tool to help measure differences in protocols of mental health randomized controlled trials. *Dialogues Clin Neurosci* 2011;13:209-215.

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## **EVALUATION OF TREATMENT PATTERNS OF MEDICAID INSURED PATIENTS WITH SCHIZOPHRENIA WHO INITIATE TREATMENT WITH EXTENDED RELEASE PALIPERIDONE PALMITATE**

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**Background:** Extended-release paliperidone palmitate is a 2nd generation injectable antipsychotic indicated for the treatment of schizophrenia [1, 2]. However, data are lacking on the treatment patterns and dose distribution of paliperidone palmitate in a naturalistic setting.

**Objectives:** To evaluate the treatment patterns and dose distribution of extended-release injectable paliperidone palmitate among Medicaid insured patients with schizophrenia.

**Methods:** Adult patients with schizophrenia (≥18 years) with at least 1 inpatient claim or 2 outpatient claims on separate dates with a primary or secondary diagnosis of ICD-9-CM code 295.X before initiating paliperidone palmitate (index event) were identified from the *MarketScan® Research* database (7/1/2008-9/30/2011). Patients were required to have 12 months of continuous Medicaid insurance enrollment before the index event. During the follow-up period (i.e after initiation of paliperidone palmitate), patients were followed until the end of Medicaid enrollment or a period of fourteen months, whichever occurred first.

**Results:** Among patients in the study cohort (N=1,578), mean age was 39 years, 56% were male, 44% were Caucasian, and 49% were African American. Prior to initiating paliperidone palmitate, nearly half (49%) of schizophrenia patients had previously used other extended-release injectable antipsychotics, of which the most frequently used were risperidone (28%) and haloperidol (17%). Prior to paliperidone

initiation, patients also received oral atypical antipsychotics including risperidone (38%), quetiapine (27%), and paliperidone (26%). Mean dosages of the first and second paliperidone palmitate injections were 193 mg and 156 mg, respectively, with the following 12 doses ranging 157 to 172 mg. The mean number of days between injections ranged 30-33 days.

**Conclusion:** This is one of the first studies that evaluates the treatment patterns and dose distribution of paliperidone palmitate in a naturalistic setting. Further analyses are needed to investigate the reasons related to this treatment pattern, as well as patient outcomes and direct treatment costs associated with the actual dose distribution of paliperidone palmitate in a naturalistic setting.

**Learning Objectives:**

- To identify characteristics of schizophrenia patients who initiate treatment with extended-release injectable paliperidone palmitate
- To evaluate the real-world dosage of extended-release injectable paliperidone palmitate among Medicaid insured patients with schizophrenia

**Source of Funding:**

Otsuka America Pharmaceutical, Inc. and H. Lundbeck A/S

**Literature References:**

- Kim S, et al. Paliperidone palmitate injection for the acute and maintenance treatment of schizophrenia in adults. *Patient Prefer Adherence*. 2012;6:533-45.
- Product Information: Invega Sustenna. Janssen Pharmaceuticals, Inc. 8/2012. [www.invegasustenna.com/pdf/invegasustenna-prescribing-info.pdf](http://www.invegasustenna.com/pdf/invegasustenna-prescribing-info.pdf)

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**MEMANTINE EFFECTS ON MATRICS CONSENSUS COGNITIVE BATTERY PERFORMANCE IN HEALTHY ADULTS AND SCHIZOPHRENIA PATIENTS**

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**Background:** Cognitive deficits contribute to functional disability in schizophrenia. Memantine is a partial NMDA antagonist and pro-cognitive agent; reports differ in its effects on schizophrenia symptoms. We tested the effects of memantine on MATRICS Consensus Cognitive Battery (MCCB) performance in healthy individuals (NCS) and schizophrenia patients.

**Methods:** The effects of 10 mg memantine on MCCB performance (T-scores for composite (Comp) and 7 domains: speed of processing (SP), attention/vigilance (A/V), working memory (WM), verbal learning (VerL), visual learning (VisL), reasoning/problem solving (R/PS), and social cognition (SC)) were evaluated in 15 NCS and 20 schizophrenia patients in an ongoing, double-blind, placebo-controlled crossover design.

**Results:** At baseline, significant performance deficits were detected in patients in the MCCB Comp score ( $p < 0.0015$ ), and in domains of SP, A/V, WM, VisL and VerL ( $p$ 's  $< 0.05$ - $0.0005$ ). In patients, Comp scores correlated significantly with GAF (Global Assessment of Function) scores ( $p < 0.02$ ), as did scores for VerL ( $p < 0.02$ ) and SC ( $p < 0.05$ ). ANOVA of MCCB revealed significant effects of diagnosis ( $p < 0.002$ ) and domain ( $p < 0.0001$ ), and a significant interaction of dose x domain ( $p < 0.045$ ), reflecting small effect size increases (VerL ( $d = 0.28$ )) and decreases (VisL ( $d = 0.22$ )) across domains in both NCS and patients.

**Conclusions:** A single, acute dose of memantine did not significantly alter composite MCCB scores, but tended to elevate domain scores (VerL) most associated with global function in patients. We are presently studying effects of higher memantine doses on MCCB performance in patients, and will assess the ability of memantine to augment the therapeutic impact of cognitive interventions.

**Learning Objectives:**

- Not published
- Submitted for Poster at SOBP 2013

- Neurocognitive Impairments in Schizophrenia

#### Source of Funding:

#### Literature References:

- Methods for Improving Neurocognition in Schizophrenia

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### **EVP-6124, AN ALPHA-7 NICOTINIC PARTIAL AGONIST, PRODUCES POSITIVE EFFECTS ON COGNITION, AND CLINICAL FUNCTION IN PATIENTS WITH CHRONIC SCHIZOPHRENIA ON STABLE ANTIPSYCHOTIC THERAPY**

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<sup>1</sup>EnVivo Pharmaceuticals

It is well recognized that patients with schizophrenia have persistent cognitive deficits despite treatment with antipsychotics. Alpha-7 nicotinic acetylcholine receptor agonists (N-A7A) are of interest as potential procognitive therapy. These receptors may be linked to various domains of cognition, including attention and long term and working memory.

EVP-6124 is a novel, potent, and selective N-A7A. Nine clinical studies with EVP-6124 have been completed in 561 unique subjects (403 received EVP-6124, 158 received placebo). EVP-6124 was safe and well-tolerated and exhibited linear kinetics with a long half-life (>60 hours) suitable for once daily dosing.

**Methods:** A Phase 2b study in stable subjects with schizophrenia (n=319) receiving atypical antipsychotics has been completed. The study assessed the safety and efficacy of two doses of EVP-6124 (0.3 and 1 mg) versus placebo. Efficacy was evaluated by the Overall Cognition Index (OCI) from the CogState testing battery and Trails 2 and 4 of the Neuropsychological Test Battery (NTB) (all subjects), the MATRICS Consensus Cognitive Battery (MCCB) (US subjects only), the Schizophrenia Cognition Rating Scale (SCoRS) and the Positive and Negative Syndrome Scale (PANSS). Statistical results, as defined in the protocol, were considered significant at  $P < 0.10$  (one-sided tests).

**Results:** Stable subjects with schizophrenia, both smokers and non-smokers, were treated with placebo (n=106), 0.3 mg (n=107) or 1 mg (n=106) of EVP-6124 for a total of 84 days.

The drug was well tolerated with no clinically significant findings with respect to ECGs, vital signs, hematology and serum chemistry or suicidal ideation and behavior. A total of 192 treatment-emergent adverse events (TEAEs) were reported in 101 (31.9%) subjects, including 25 (23.4%) subjects in the 0.3 mg group, 35 (33.3%) subjects in the 1 mg group, and 41 (39%) subjects in the placebo group. The most commonly reported TEAEs were headache (3.8%), nausea (3.2%) and nasopharyngitis (2.5%). The incidence of serious adverse events was similar among the three dosing groups; none were judged related to drug.

The OCI plus Trails 2 and 4 suggested that 0.3 mg of EVP-6124 compared to placebo, was associated with improvement in general cognitive function ( $P = 0.034$ ) and that this improvement was due mainly to the beneficial effects of the drug on visual learning, visual attention, and social cognition. This positive effect on the OCI was supported by a strong positive trend (NS) for improved cognition on the MCCB Battery which was performed only in the US (n=166). For the 1 mg group, the mean change from baseline at day 84 in the overall Composite T-score and the associated percentile change were higher than for the 0.3 mg group and placebo.

Significant effects in clinical function were also seen with EVP-6124 as measured by the SCoRS Interviewer Rating of clinical function over all visits for the 1 dose group compared to the placebo ( $P = 0.065$ ).

**Discussion:** In this study, EVP-6124 treatment of subjects with schizophrenia resulted in improved cognition and clinical function. EVP-6124 was well tolerated in this population. These data support the continued investigation of EVP-6124 in larger confirmatory trials which are currently ongoing.

#### Learning Objectives:

- Investigation of procognitive effects of a novel agent in patients with schizophrenia

- Measures of cognitive function and potential treatment effect in a clinical trial of subjects with schizophrenia

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## COMPARISON OF RESTING STATE DYNAMICS IN HEALTHY, SCHIZOPHRENIA AND BIPOLAR DISEASE

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**Purpose:** In this work, we compare the dynamics of resting state fluctuations in healthy controls (HC), and age-matched samples of patients with schizophrenia (SZ) and bipolar disorder (BP). The primary objective of this study was to examine the differences in temporal dependence of whole-brain functional network connectivity (FNC) ([Jafri et al., 2008](#)), defined as pairwise correlation between timecourses of intrinsic connectivity networks (ICNs) obtained using spatial independent component analysis (ICA), using a sliding-window correlation approach ([Allen et al., 2012](#)). Secondary objectives include characterizing the differences in transition probabilities between FNC states as well as to investigate the associations of the dynamic measures with clinical symptoms.

**Methods:** In this study we used resting-state functional magnetic resonance imaging data from 159 subjects which include 61 HC, 60 SZ and 38 BP subjects matched for age. Data included 210 volumes of resting data (TR = 2 sec) collected while the subjects were lying down with eyes open on a 3 T Siemens scanner. After initial standard preprocessing, the imaging data was decomposed into spatial maps exhibiting temporally coherent activity using a high model order (100) group-level spatial ICA. Out of the 100 components obtained, we visually identified 49 components as ICNs. Subject specific time courses and spatial maps were obtained using back reconstruction approach. Subsequently we computed correlations between ICN timecourses using whole time course (static FNC) as well as using a sliding temporal window (Tukey window having a width of 44 s; sliding in steps of 1 TR) to capture the variability in connectivity as described in Allen et al., 2012. The dynamic windowed FNC matrices were clustered using K-means algorithm to study patterns of reoccurring states. We determined the number of clusters to be 5 using the elbow criterion of the cluster validity index computed as the ratio between within-cluster distances to between-cluster distance. Group and subject specific centrotypes were computed. Subject specific centrotypes were used to perform independent sample *t*-tests to probe for group differences.

**Results:** No significant group differences were observed in static FNC in this sample. Dynamic FNC analysis in contrast suggests that patients make fewer transitions to some states (States 2 and 4) compared to healthy controls; i.e. patients spent less time in a highly intercorrelated state, and more time in a state where various brain regions were loosely correlated. Initial results also demonstrate a few significant differences between groups in some dynamic FNC states between HC and BP subjects as well as HC and SZ subjects.

**Conclusions:** The whole-brain FNC dynamics can be well estimated using the sliding-window approach. By clustering the windowed FNC matrices, we are able to identify differences in patterns of FNC that are not recognized using the static FNC method. This study gives results which may help us differentiate between different patient groups. Further study of FNC dynamics in both resting-state and task-related data for different groups will provide an important tool to better understand the brain changes associated with mental illness.

### Learning Objectives:

- The audience should be presented with high dimensional, static resting state fMRI analyses and its application to distinguishing schizophrenia and bipolar disorder.
- The audience should be presented with dynamic resting state fMRI analyses and its application to schizophrenia and bipolar disorder.

**Source of Funding:** NIH/NIBIB: 2R01 EB000840-06

**Literature References:**



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## **HOSPITALIZATION RATES IN PATIENTS PREVIOUSLY TREATED WITH ORAL ANTIPSYCHOTICS VS. PROSPECTIVELY TREATED WITH ARIPIRAZOLE ONCE-MONTHLY: A MIRROR STUDY**

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**Objective:** To assess hospitalization rates in a mirror study (6 months pre- and post- switch), in patients with schizophrenia treated prospectively with the investigational agent aripiprazole once-monthly 400 mg (ARI-OM-400; an extended-release injectable suspension) compared with the same patients previously treated with oral antipsychotics.

**Methods:** A multicenter, open-label mirror study in patients with schizophrenia treated in a naturalistic community setting. Eligible patients were aged 18–65 years with a current diagnosis of schizophrenia (DSM-IV-TR criteria), a history of illness (>1 year), and 7 months of hospitalization history. Patients must not have been hospitalized within the last 4 weeks. Eligible patients entered a conversion phase (Phase A; up to 4 weeks) where they were cross-titrated to oral aripiprazole (ARI) monotherapy, if necessary, and thereafter a 24-week, open-label treatment phase (Phase B), where patients received ARI-OM-400 (option to decrease to 300 mg), while receiving concomitant oral ARI for the first 14 days of Phase B. The primary endpoint was to compare psychiatric hospitalization rates (proportion of patients with  $\geq 1$  inpatient psychiatric hospitalization) between the retrospective oral antipsychotic treatment (last 3 months before oral conversion [i.e. Month 4 to 6]) and the prospective ARI-OM-400 treatment period (last 3 months [i.e. Month 4 to 6 after ARI-OM-400 initiation]) in patients treated with ARI-OM for at least 3 months. Safety and tolerability were assessed.

**Results:** The current interim analysis (November 16, 2012), is based on data from 227 patients, of which 183 entered Phase B and 101 completed Phase B. The primary endpoint was calculated for 121 subjects who had completed  $\geq 3$  months treatment in Phase B. The hospitalization rates for inpatient psychiatric hospitalization at Months 4–6 were lower following the switch to ARI-OM-400 (6.6%; n=8/121) compared with the retrospective treatment period when the same patients were treated with oral antipsychotics (28.1%; n=34/121). The rate of inpatient psychiatric hospitalization in the prospective period only was 2.5% (n=3/121), while the rate of inpatient psychiatric hospitalization in the retrospective period only was 24% (n=29/121) ( $p<0.0001$ , Exact McNemar's test). All-cause discontinuations during the prospective Phase B were 44.8% (n=82/183). The most common reasons for discontinuation in Phase B were: subject withdrew consent, 15.3% (n=28/183); adverse events, 14.2% (26/183); and patient lost to follow up, 7.1% (n=13/183). Treatment-emergent adverse events with  $>5\%$  incidence (Phase B safety sample; n=181) were psychotic disorder (7.7%), akathisia (7.2%), insomnia (7.2%) and paranoid schizophrenia (5.5%).

**Conclusions:** Treatment with ARI-OM-400 significantly reduced the rate of psychiatric hospitalizations compared with previous antipsychotic treatment.

### **Learning Objectives:**

- Understand the effect of the investigational drug aripiprazole once-monthly on hospitalization rates

- Understand the design of a mirror study to investigate the effect of aripiprazole once-monthly on symptoms and patient functionality

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

**Literature References:**

- Kane et al. J Clin Psych 2012;73:317–624
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**EFFICACY OF CARIPRAZINE ON PANSS ITEMS AND MARDER FACTORS: POST HOC ANALYSIS OF A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN SCHIZOPHRENIA**

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**Background:** Schizophrenia is a multidimensional disorder comprising positive, negative, and mood symptoms as well as cognitive deficits. Potent occupancy and modulation of both dopamine D<sub>3</sub> and D<sub>2</sub> receptors may confer broad efficacy across the range of schizophrenia symptoms. Cariprazine (CAR), an orally active and potent dopamine D<sub>3</sub>/D<sub>2</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors, is currently in development for the treatment of schizophrenia and bipolar mania. Primary and post hoc analyses of PANSS data from a Phase III study (NCT01104779) evaluated the efficacy and safety of CAR in patients with acute exacerbation of schizophrenia.

**Methods:** Patients were randomized to 6 weeks of double-blind treatment with placebo (PBO), CAR 3-6 mg/d, or CAR 6-9 mg/d. The primary and secondary efficacy parameters were change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impressions-Severity (CGI-S) score, respectively, analyzed using an MMRM approach adjusting for multiple comparisons. Post hoc analyses evaluated efficacy on PANSS-derived Marder factor groupings (negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, anxiety/depression) and PANSS single items; post hoc analyses did not adjust for multiple comparisons. Safety assessments included treatment-emergent AEs (TEAEs), laboratory values, vital signs, ophthalmology assessments, ECG, and EPS scales.

**Results:** Of the 446 patients that were randomized and received treatment (PBO=147; CAR 3-6 mg/d=151; CAR 6-9 mg/d=148), 60.5% completed the study. The most common reasons for discontinuation were withdrawal of consent (16.4%), insufficient therapeutic response (11.4%), and AEs (9.0%). The least squares mean difference (LSMD) vs PBO in PANSS total score at Week 6 was -6.8 ( $P=.0029$ ) for CAR 3-6 mg/d and -9.9 ( $P<.0001$ ) for CAR 6-9 mg/d. The LSMD vs PBO on CGI-S scores was significant at Week 6 for both CAR 3-6 mg/d (-0.3,  $P=.0115$ ) and CAR 6-9 mg/d (-0.5,  $P=.0002$ ). The LSMD vs PBO was also significant ( $P<.05$ ) for CAR 6-9 mg/d on all 5 Marder factor groupings; CAR 3-6 mg/d was significant on most factors. On PANSS single items, the LSMD vs PBO was significant ( $P<.05$ ) on 21 of 30 items for CAR 6-9 mg/d and on 11 of 30 items for CAR 3-6 mg/d. Common TEAEs ( $\geq 5\%$  and twice the rate of PBO) seen in both CAR groups were akathisia, EPS, and tremor; most were mild to moderate in severity.

**Conclusion:** CAR was significantly superior to placebo on PANSS total score, across Marder factors, and on many PANSS single items, suggesting broad efficacy in the treatment of schizophrenia. CAR was generally well tolerated, although the incidence of EPS-related TEAEs was greater for CAR than PBO.

**Learning Objectives:**

- Gain understanding of the broad efficacy profile of cariprazine in the treatment of schizophrenia
- Better understand the safety and tolerability of cariprazine in patients with schizophrenia

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

**Literature References:**

- Kiss B, Horváth A, Némethy Z, Schmidt E, Laszlovszky I, Bugovics G, Fazekas K, Hornok K, Orosz S, Gyertyán I, Agai-Csongor E, Domány G, Tihanyi K, Adham N, Szombathelyi Z: Cariprazine (RGH-188), a dopamine D3 receptor-preferring, D3/D2 dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. *J Pharmacol Exp Ther.* 2010;333(1):328-340.
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## BROAD THERAPEUTIC POTENTIAL FOR ITI-007 AND IC200131

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**Background:** ITI-007 is an investigational new drug that represents a unique approach to serotonergic, dopaminergic, and glutamatergic modulation, with differing pharmacology depending on dose. *In vitro*, ITI-007 is a potent serotonin 5-HT<sub>2A</sub> receptor antagonist with approximately 60-fold separation between 5-HT<sub>2A</sub> and other neuropharmacological targets. As its concentration is increased, ITI-007 exhibits cell-type specific modulation of dopamine D<sub>2</sub> receptors. *In vivo*, ITI-007 acts as a pre-synaptic partial agonist and post-synaptic antagonist with mesolimbic/mesocortical selectivity. Along with cell-type specific dopaminergic modulation, higher concentrations of ITI-007 increases phosphorylation of mesolimbic GluN2B subunits of N-methyl-D-aspartate (NMDA) channels, consistent with enhancement of glutamatergic neurotransmission, and inhibits serotonin reuptake. Together, these data suggest different therapeutic utility at low doses of ITI-007 compared to higher doses. Adding to this unique profile, ITI-007 is metabolized into IC200131, a serotonin-2A (5-HT<sub>2A</sub>) receptor antagonist and inhibitor of serotonin reuptake with roughly equal potency at each of these two targets. Interestingly, IC200131 is back-converted into ITI-007. The pharmacology of IC200131 was explored further *in vivo* in preclinical models.

**Methods:** Orally administered IC200131 was evaluated for its ability to reduce head-twitch behavior induced by a 5-HT<sub>2A</sub> receptor agonist (quipazine) and to reduce amphetamine-induced hyperactivity in rodents.

**Results:** In rodents, IC200131 reduced quipazine-induced head-twitches and inhibited amphetamine-induced locomotor activity, consistent with 5-HT<sub>2A</sub> receptor antagonism and antipsychotic efficacy, respectively.

**Discussion:** The pharmacological activity of IC200131 and back-conversion of IC200131 into ITI-007 extends the effective half-life and enhances the therapeutic potential of ITI-007. Moreover, IC200131 was selected as a development candidate as a treatment for mood symptoms associated with neuropsychiatric and neurological disorders. It is anticipated that the 5-HT<sub>2A</sub> receptor antagonist properties of IC200131 will lead to improved sleep, reduced aggression and better impulse control. Serotonin reuptake inhibition induced by IC200131 will reduce depression and other dysthymic symptoms, while its 5-HT<sub>2A</sub> receptor antagonism will enhance antidepressant efficacy and reduce sexual side effects. Through its conversion to ITI-007, IC200131 gains dopaminergic protein phosphorylation modulator activity and glutamatergic protein phosphorylation modulation. The combined actions of IC200131 and ITI-007 present a novel pharmacologic profile that may have broad utility in treating neuropsychiatric and related disorders. ITI-007 is in Phase 2 clinical development for acute and residual schizophrenia and IC200131 is currently in preclinical development.

### Learning Objectives:

- To better understand the unique pharmacological profile of ITI-007, an investigational new drug.
- To better understand the behavioral effects of IC200131, a metabolite of ITI-007, and its contributions to the unique pharmacology of ITI-007.

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## ONSET OF EFFICACY IN SCHIZOPHRENIA SYMPTOM DOMAINS WITH LONG-ACTING INJECTABLE PALIPERIDONE PALMITATE VS ORAL RISPERIDONE

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**Introduction:** As schizophrenia presents with diverse symptoms, evaluating the effects of antipsychotics on different symptoms or domains is important for effective treatment decisions. This secondary analysis of a database from a double-blind study (NCT00589914) of paliperidone palmitate (PP; no oral supplementation) and risperidone long-acting injection (RLAI; with oral risperidone supplementation) evaluated the onset of efficacy by symptom domain as determined by PANSS factor scores.

**Methods:** Subjects received (a) PP (n=453; 234 mg day 1 and 156 mg day 8, followed by once-monthly flexible dosing) and RLAI-matched placebo injections or (b) RLAI (n=460; 25 mg days 8 and 22, followed by biweekly flexible dosing) and PP-matched placebo injections. RLAI subjects received oral risperidone on days 1–28, whereas PP subjects received oral placebo. Because of RLAI's release profile and injection regimen, effects through day 28 in the RLAI arm were effectively due to oral risperidone only. Assessments included PANSS factor scores at days 4, 15, and 22 (LOCF). Paired *t*-tests evaluated within-group differences, and ANCOVA evaluated between-group differences.

**Results:** All PANSS factor scores (positive, negative, disorganized thoughts; uncontrolled hostility/excitement; and anxiety/depression) improved significantly with PP and oral risperidone by day 4 through day 22 ( $P<0.001$  for all within-group changes). Mean (SD) PANSS factor score changes from baseline to day 22 for PP and oral risperidone were positive (–3.5 [4.0] and –3.2 [3.9]), negative (–2.3 [3.2] and –2.3 [3.4]), and disorganized thoughts (–2.0 [3.1] and –1.8 [2.7]); uncontrolled hostility/excitement (–1.4 [2.4] and –1.3 [2.4]); and anxiety/depression (–2.0 [2.3] and –1.7 [2.3]). The only between-group differences during this period were observed at day 4 in PANSS positive (LS mean [SE] change for PP vs oral risperidone: –0.8 [0.1] vs –0.6 [0.1];  $P=0.02$ ) and disorganized thoughts (–0.5 [0.1] vs –0.3 [0.1];  $P=0.04$ ) factor scores. Treatment-emergent adverse events during early time points were described by Gopal et al.

**Conclusion:** The timing and pattern of efficacy responses with injectable PP appeared similar to those observed with oral risperidone during the first month of treatment in symptomatic subjects with schizophrenia. All mean PANSS factor scores improved significantly in both groups by first assessment at day 4; some between-group differences favored PP without oral supplementation.

### Learning Objectives:

- To understand the need to evaluate the effects of antipsychotics on different symptom groupings or domains in patients with schizophrenia
- To understand the extent of the onset of efficacy with paliperidone palmitate compared with oral risperidone in schizophrenia symptom domains

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

### Literature References:

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- Pandina G, Lane R, Gopal S, Gassmann-Mayer C, Hough D, Remmerie B, Simpson G. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:218-226.

## REFRESH: A PHASE2 RP 5063 EFFICACY AND SAFETY IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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**Background:** RP5063 is a new atypical antipsychotic Dopamine-Serotonin System Stabilizer with partial agonist activity at D2, D3, and D4 receptors, partial agonist activity at 5-HT1A and 5-HT2A receptors, and antagonist activity at the 5-HT7 receptor. It has high affinity for D2S, D2L, D3, D4, 5-HT1A, 5-HT2A, 5-HT7 and H1 receptors at low nM concentrations, moderate affinity for D1, D5, 5-HT3, 5-HT6, SERT, and alpha1B receptors with no significant affinity for 5-HT1B, alpha2, H3, M3, AMPA and NMDA receptors or DAT, NET, AChE. RP5063 has no cardiovascular, pulmonary or CNS (other than exaggerated pharmacology) adverse effects in the safety pharmacology animal studies. RP5063 does not adversely alter QT interval. Phase I randomized placebo and single/multiple dose study in 56 subjects with schizophrenia showed excellent pharmacokinetics, safety and tolerability with expected adverse effect profile; enrollment in a larger global Phase 2 Safety & Efficacy study in acute schizophrenia/schizoaffective disorder is complete and the results are expected in March 2013.

**Methods:** The REFRESH Phase 2 trial was to assess the safety & efficacy of RP5063 (15mg, 30mg and 50mg) administered to subjects with an acute exacerbation of schizophrenia or schizoaffective disorder, as measured by change from baseline to Day 28 on the Positive and Negative Syndrome Scale (PANSS) total score. Each subject participated in the study for up to 7 weeks. The study comprised of a screening period (Day minus 6 to Day 0), baseline (Day 1 pre-dose) and fixed dose treatment period (Day 1 to Day 28) and follow-up visit for re-stabilization after 1 week of the last dose of study treatment (Day 35±2). Subjects between 18 and 65 years with a clinical diagnosis of acute exacerbation of schizophrenia or schizoaffective disorder (at least one year prior to screening) according to DSM-IV-TR criteria were entered. Screening score for the acute psychosis on the BPRS of >36 and BPRS psychosis cluster a minimum score of 4 or higher on at least two of the four items: suspiciousness, conceptual disorganization, hallucinatory behavior, and/or unusual thought content

**Results:** REFRESH study was conducted in Europe, Asia and the USA with 234 subjects were randomly assigned to one of the five groups: RP5063-15mg once daily (QD), RP5063-30mg (QD), RP5063- 50mg (QD), placebo (QD) or an active comparator (aripiprazole 15mg (QD)) in a ratio of 3:3:3:2:1. Subjects were hospitalized for the entire duration of study treatment. While results will be unblinded and analyzed before the meeting, at this time the blind results show good tolerability, consistent with previous Phase 1 data. Only SAEs are borderline liver enzymes elevation or infection. Broader adverse effects are in the expected range from constipation, dizziness, emesis, insomnia and EPS including akathisia. There were no safety signals identified in the clinical laboratory including prolactin and metabolic syndrome indices, vital signs, or ECG (QT changes). On the efficacy measures, PANSS total scores, PANSS sub scores, CGI, also measures of cognition and depression were gathered and will be unblinded and analyzed shortly.

**Conclusions:** Safety data gathered from the blinded trial thus far is consistent with previous Phase 1 data and points to good tolerability. Upon unblinding, the data will likely show overall evidence of safety and efficacy for RP5063 consistent with earlier clinical data in schizophrenia. Current clinical trial blind data is consistent with RP5063's unique pharmacological profile, a better safety profile and efficacy signals previously observed in Phase 1 study schizophrenia patients. A large global Phase 3 trial is planned after analysis of Phase-2 data and RP5063 is expected to offer significant advantage over existing treatments for schizophrenia.

#### **Learning Objectives:**

- To learn the safety of a new treatment in psychotic disorders
- To assess efficacy of a new treatment in psychotic disorders

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**Introduction:** A gluten hypothesis of schizophrenia has been proposed based on the findings of increased seroprevalence and serointensity of antibodies to the wheat protein gliadin, in schizophrenia patients relative to healthy controls (Okusaga et al 2012). However, the few clinical trials of gluten-free diet in schizophrenia conducted in the past yielded contradictory results (Kaladjian et al 2006). An important limitation of these trials is that the anti-gliadin status of the participants was not evaluated. As it is likely that gluten-free diet will be beneficial to only a subset of schizophrenia patients (i.e. those seropositive for anti-gliadin) it is important to further evaluate the effect of gluten-free diet in schizophrenia patients that have also been demonstrated to have immune sensitivity to gluten. To date, only one study has been conducted to evaluate the effect of gluten-free diet in schizophrenia patients screened for gluten sensitivity; and as this study involved 2 participants (only one was positive for anti-gliadin IgG) assessed for 2 weeks (Jackson et al 2012), more studies are urgently needed. This study aims to compare, in schizophrenia patients experiencing acute exacerbation of symptoms, combined antipsychotic medication and gluten-free diet versus antipsychotic medication and regular (i.e. gluten-containing) diet, in terms of symptomatic improvement and safety.

**Methods:** This randomized parallel-group prospective study of antipsychotic augmentation with gluten-free diet in acute exacerbation of schizophrenia will be conducted at the University of Texas Harris County Psychiatric Center (HCPC), Houston, Texas. Inclusion criteria are: male and female gender, DSM-IV diagnosis of schizophrenia, seropositivity for anti-gliadin IgG, age 18 to 60 years, PANSS total score  $\geq 70$  and  $\leq 120$  and negative pregnancy test in females. Exclusion criteria are: DSM-IV diagnoses of schizoaffective disorder, bipolar disorder, schizophreniform and other psychotic disorders, pervasive developmental disorder, dementia, delirium, other cognitive disorders, suicidal and homicidal ideations. In addition to prescribed antipsychotics, participants will be randomly assigned to receive either a gluten-free diet or regular (i.e. gluten-containing) diet for 2 weeks. The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) will be used to rate symptom severity and the efficacy outcome measure will be change in PANSS from baseline. Given the resource limitations associated with this proposal, a fixed sample size per group ( $n=10$  / group) is proposed. Power was set at .80 and the alpha level set to 0.05. A sigma value of 10 points was estimated from Chan et al 2007 (Figure 2). Using these values results in this project being able to detect a treatment effect of 13.3 points (or greater) between gluten-free and regular diet groups. Variables found to differ between groups at baseline will be included as additional covariates in the, two-group, Analysis of Covariance (ANCOVA). The baseline PANSS score will be entered as the covariate in the analysis of two-week PANSS scores.

**Discussion:** If gluten-free diet is shown to be efficacious, safe and tolerable in anti-gliadin antibody-positive schizophrenia patients, this may lead to its recommendation as part of the treatment regimen in schizophrenia (as is done for celiac disease).

**Learning Objectives:**

- Has not been published previously.
- Has not been previously presented.
- Attendees will become familiar with the literature on the association of schizophrenia with gluten sensitivity.

**Source of Funding:**

**Literature References:**

- Kalaydjian AE, Eaton W, Cascella N, Fasano A. The gluten connection: the association between schizophrenia and celiac disease. *Acta Psychiatr Scand.* 2006 Feb;113(2):82-90.
- Attendees will become aware of emerging data on the potential utility of gluten-free diet in schizophrenia.

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**Objective:** Sedation is a common side effect of many antipsychotics. The objective of this analysis was to evaluate the effects of two atypical antipsychotic agents on daytime sleepiness during 6 months of flexible dose treatment with lurasidone or quetiapine XR in a double-blind study. The role of daytime sleepiness as a mediator of changes in cognitive performance was also evaluated.

**Methods:** This double-blind, continuation study included subjects who had completed an initial randomized, double-blind, 6-week trial. Subjects received continued treatment with flexible once-daily doses of lurasidone (40-160 mg; n=151, LUR-LUR) or quetiapine XR (200-800 mg; n=85, QXR-QXR). Subjects initially treated with placebo were started on flexible once-daily doses of lurasidone 40-160 mg (n=56). Sedation was assessed using the Epworth Sleepiness Scale (ESS), a validated patient self-report measure of daytime sleepiness. Cognitive performance was examined with the computerized CogState battery at baseline, 6 weeks, and 3 and 6 months in the extension phase.

**Results:** Mean changes in ESS total score from core baseline to week 6 (end of acute phase) were -0.71 (SE 0.35) for LUR-LUR versus +0.26 (SE 0.48) for QXR-QXR ( $p<0.05$ ). The treatment difference in ESS total score between LUR-LUR and QXR-QXR was maintained at week 32 (month 6 of extension) ( $p=0.03$ ), with significantly lower sleepiness in the LUR-LUR group (LS Mean 4.4, SE 0.2) compared to the QXR-QXR group (LS Mean 5.9, SE 0.3). Subjects treated with lurasidone showed a significantly higher cognitive performance compared to quetiapine XR at months 3 ( $p<0.05$ ) and 6 of the extension ( $p<0.05$ ). There was a significant association between changes in ESS total score and CogState cognitive composite score from acute phase baseline to week 32, with increase in ESS total score associated with lower cognitive performance ( $p<0.05$ , longitudinal mixed effects model). Statistical interaction test showed that the relationship between changes in ESS and cognitive performance was similar for both lurasidone and quetiapine XR groups at week 32 ( $p>0.05$  for treatment-by-change in ESS score).

**Conclusion:** Treatment with 80 mg or 160 mg of lurasidone, administered once-daily in the evening, was associated with significantly less sedation compared with quetiapine XR (200-800 mg/d) over 6 months of treatment, assessed using the ESS. Increased daytime sleepiness was significantly associated with lower cognitive performance. Future research to examine the extent to which daytime sleepiness impacts functional capacity and quality of life is warranted.

#### **Learning Objectives:**

- To characterize daytime sleepiness in lurasidone and quetiapine XR treated patients with schizophrenia, using the Epworth Sleepiness Scale (ESS).
- To evaluate the long-term impact of daytime sleepiness on cognitive performance.

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

#### **Literature References:**

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#### **AN ANALYSIS OF PATIENT AND PRESCRIBER PERSPECTIVES ON LONG-ACTING ANTIPSYCHOTICS FOR SCHIZOPHRENIA BASED ON IN-OFFICE DISCUSSIONS**

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**Purpose:** Long-acting injectable antipsychotics (LAIs) have been associated with reduced relapse rates, hospitalizations, and costs of care. However, they are underused and often reserved for schizophrenia

patients who are late in the course of disease and/or nonadherent to treatment. Patient and prescriber perspectives may present both obstacles to and opportunities for LAI use. This study examined prescriber-patient interactions to further understand their perspectives to facilitate improved clinical approaches when using LAIs.

**Methods:** Patients had a primary *DSM-IV* diagnosis of schizophrenia. Patient/caregiver and prescriber (psychiatrists, nurse practitioners [NPs]) interactions during treatment visits were recorded from August 2011–February 2012 at 4 community mental health centers (CMHCs) in the United States. Conversations were transcribed and analyzed. Discussion was categorized according to 11 predetermined topics occurring in a typical CMHC visit. This study included 22 patients who were being treated with oral antipsychotics and 38 who were being treated with LAIs.

**Results:** In 69 prescriber-patient conversations (psychiatrist, n=60; NPs, n=9) treatment discussion and behavior modification/counseling occupied >50% of the visit and adherence occupied 2%. Prescriber-patient visits averaged 12 minutes for psychiatrists and 9 minutes for NPs. Overall, treatment decisions were made without patient/caregiver input in 40 of 60 conversations (67%). Patients with less severe impairment were more likely to be involved in treatment decision. In patients offered an LAI (N=19), 11 (58%) accepted LAI treatment irrespective of whether their perceptions about LAIs were favorable, neutral/passive, or unfavorable. Of the subset of patients who were neutral/passive, 67% were prescribed an LAI. Of those patients who had an unfavorable/concerned perception, 29% were prescribed an LAI. In the LAI naïve group, the main concerns of the prescribers were mainly about their fear of damaging the therapeutic relationship and drug side effects. The patient-expressed reasons for refusing LAI treatment were fear of needles, dosing logistic/administration, and side effects. Psychiatrists sometimes overcame patient LAI objections by decomposing resistance, uncovering resistance severity, and investigating beyond stated problems to address root issues. Patient-perceived LAI benefits included rapid symptom improvement and greater overall efficacy.

**Conclusions:** This study characterized prescriber-patient interactions and perspectives on LAI treatment. More than half of LAI-naïve patients were amenable to LAI therapy due to their positive or neutral stance on treatment. There is opportunity to increase active patient engagement, address barriers, and provide better LAI-relevant information to individualize and broaden treatment options and approaches in the patient with schizophrenia.

#### **Learning Objectives:**

- Describe the concerns of patients and prescribers regarding long-acting injectable antipsychotics.
- Review means by which resistance to the use of long-acting injectable antipsychotics may be addressed.

#### **Source of Funding:**

Otsuka America Pharmaceutical Inc. and H. Lundbeck A/S

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### **AZD8529, A POSITIVE ALLOSTERIC MODULATOR AT THE MGLUR2 RECEPTOR, DOES NOT IMPROVE SYMPTOMS IN SCHIZOPHRENIA: A PROOF OF PRINCIPLE STUDY**

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**Introduction:** Aberrant cortical connectivity and hypofunction of NMDA receptor signaling may underlie some schizophrenia symptoms. Direct activation of mGluR2/3 receptors has been shown to reduce effects of NMDA antagonists in animal studies. In humans, this mechanism has been shown to reduce the working memory deficit induced by ketamine; one study showed an antipsychotic effect in



acute schizophrenia, an effect not reproduced in subsequent studies. We have investigated the efficacy and tolerability of AZD8529, a selective positive allosteric modulator (PAM) at the mGluR2 receptor, in symptomatic patients with schizophrenia.

**Methods:** Following 7 days washout, patients were randomized to receive either AZD8529 40mg (n=61), risperidone 4mg (n=31), or placebo (n=60) for 28 days. Clinical efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression –Severity (CGI-S) and –Improvement (CGI-I) Scales as primary outcome measures. Change from baseline to endpoint was analyzed by MMRM methods.

**Results:** Baseline PANSS did not differ between groups (AZD8529: 92.9; placebo: 93.6; risperidone: 91.0). After 28 days of treatment there was no significant difference between the AZD8529 and placebo groups in the PANSS total score change from baseline ( $\Delta=1.8$ ,  $p=0.41$ ). Reductions in PANSS total score were significantly greater for risperidone as compared to placebo ( $\Delta=-9.8$ ,  $p<0.001$ ). Similarly, significant differences versus placebo were observed for risperidone but not AZD8529 for the PANSS subscale and CGI-S scores.

**Conclusions:** This single dose study does not support a role for positive modulation of mGluR2 receptors as a mechanism for monotherapy to treat acute schizophrenia. It remains to be determined whether different treatment regimens or adjunct treatment would provide benefit.

**Learning Objectives:**

- To understand the glutamate hypothesis of schizophrenia and its implication for the pharmacotherapy for schizophrenia.
- To be knowledgeable regarding development of therapeutic agents for schizophrenia whose mechanisms involve activation of metabotropic glutamate receptors.

**Source of Funding:**

N/A

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**EARLY DEVELOPMENT OF ALKS 3831: A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF SCHIZOPHRENIA**

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A number of antipsychotic medications are associated with weight gain and significant adverse metabolic effects.<sup>1</sup> Additionally, schizophrenia is associated with a high incidence of comorbid substance abuse. Both of these factors are obstacles in the treatment and management of many patients with schizophrenia thus limiting patient adherence to medication and adversely impacting treatment outcomes.<sup>1,2</sup> Therefore, a medication that is effective in treating symptoms of schizophrenia with an improved safety and tolerability profile may be a useful addition to the therapeutic armamentarium.

Olanzapine (OLZ) is regarded as one of the most effective treatments for schizophrenia, but concerns with weight gain and adverse metabolic effects have affected physician prescribing and patient adherence to OLZ treatment.<sup>1</sup>

ALKS 33, a novel opioid modulator, acts as an antagonist at  $\mu$  opioid receptors, with mixed agonist/antagonist activity at  $\kappa$  and  $\delta$  receptors. Nonclinical studies suggest that ALKS 33 may be useful in mitigating or preventing OLZ-induced weight gain. Using a standard rodent model, it was demonstrated that co-administration of ALKS 33 mitigated OLZ-induced weight gain, whereas naltrexone did not.<sup>3</sup> In a subsequent study using non-human primates to investigate OLZ-induced changes in weight

gain or metabolic effects, ALKS 33 attenuated OLZ-induced weight gain and fat accretion following 28-days of repeat daily dosing.<sup>4</sup>

ALKS 3831, a novel drug candidate, is a fixed-combination of ALKS 33 and OLZ currently under development for the treatment of schizophrenia. This formulation is intended to confer a more favorable safety profile compared to OLZ alone. Additionally, by virtue of its pharmacology, ALKS 33 may present additional benefits to patients with schizophrenia comorbid with substance abuse/dependence. To investigate the safety and effect on weight of ALKS 3831 in comparison to OLZ, a Phase I study in healthy, normal weight (BMI 15-25) male volunteers was conducted. Subjects were randomized to OLZ (n=35) or ALKS 3831 (n=34). After 21 days of daily dosing, subjects were observed off treatment for 14 days. Efficacy was determined by the mean change from baseline to last treatment period assessment in body weight (kg) for OLZ vs. ALKS 3831. After 21 days of daily dosing, the mean ( $\pm$ SD) change in body weight for OLZ and ALKS 3831 was +3.4 ( $\pm$ 1.8) and +2.5 ( $\pm$ 1.4), respectively. The weight gain observed in the ALKS 3831 group was significantly less than that of the OLZ group ( $p < 0.014$ ). Overall safety and tolerability of ALKS 3831 was similar to OLZ alone.

ALKS 3831 may provide an important new treatment option for schizophrenia with an enhanced safety profile and potential utility in patients with comorbid substance abuse/dependence. Further research is warranted to explore additional doses of ALKS 3831 over longer durations in treatment populations.

#### **Learning Objectives:**

- Participants will learn about the ability of ALKS 33, a component of ALKS 3831, to attenuate OLZ-induced weight gain.
- Participants will learn about a new drug candidate, ALKS 3831, as a novel treatment for schizophrenia with attributes that may contribute to an enhanced efficacy and safety profile.

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**Background:** Prior studies of schizophrenia (SZ) and bipolar disorder (BD) have demonstrated disease specific defects of the GABAergic system in discrete regions of the human hippocampus. These changes involve aberrant expression of genes within the GAD67 regulatory network, and resultant effects on GABAergic neuronal function. To investigate the hypothesis that DNA methylation plays a prominent role in the dysregulation of this gene network in SZ and BD, we have developed a methodology to reliably assess DNA methylation within isolated hippocampal subregions dissected from post-mortem human brain.

**Methods:** Using the Illumina HumanMethylation450 Beadarray, methylation levels at >480,000 CpG sites across the genome were measured in DNA extracts from tissue microdissected from stratum oriens (SO) of regions CA3/2 or CA1 of post-mortem human hippocampus. 4 cases (2 SZ and 2 control) were included in this preliminary study.

**Results:** This methodology successfully measured methylation levels at 99.7% of the CpG sites interrogated by the assay. The assay is highly reliable, as technical replicates of control DNA yielded a correlation coefficient of 0.992. This work has produced promising data with >2 fold changes in methylation levels in schizophrenia within a subset of the genes of interest (CCND2, DAXX, GAD1, GRIK2, SMURF1). Consistent with existing gene expression data, greater variability of DNA methylation was observed in SO of CA3/2 as compared to SO of CA1.

**Conclusion:** This work has successfully established a methodology that is currently being applied to a larger cohort for comparison of methylation profiles across diagnostic categories of SZ, BD, and control.

**Learning Objectives:**

- Understand current methodologies for investigation of DNA methylation patterns and dynamics in health and psychiatric disease.
- Understand the relevance of DNA methylation and other epigenetic mechanisms to the etiology and potential treatment of psychotic disorders.

**Source of Funding:** American Psychiatric Association/Pfizer Pharmaceuticals MD/PhD Research Fellowship

Harvard Medical School Dupont-Warren Fellowship Award

NARSAD Young Investigator Award

R01 to F. Benes NIMH R01MH77175

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**SUVOREXANT: OREXIN RECEPTOR ANTAGONISM AND INSOMNIA**

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Suvorexant is a novel orexin receptor antagonist current under review by the US FDA as a potential new agent for the treatment of insomnia. The phase 3 program was recently completed, and includes 3 large studies assessing the safety and efficacy of suvorexant. The results of these studies provide evidence supporting the efficacy of suvorexant for the treatment of insomnia, including disturbances of sleep onset as with well sleep maintenance, with favorable safety and tolerability profile. The suvorexant development program and results will be discussed during this presentation.

**Learning Objectives:**

- To understand the role of orexin receptor antagonists in the treatment of primary insomnia
- To understand the efficacy, safety and tolerability of suvorexant

## THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS: EFFECTS OF FETAL EXPOSURE ON RISK FOR CONGENITAL MALFORMATIONS AND MATERNAL AND NEWBORN OUTCOMES

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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 to address this knowledge gap.

Website: [www.womensmentalhealth.org/pregnancyregistry](http://www.womensmentalhealth.org/pregnancyregistry)

**Methods:** The NPRAA was established in 2008. Potentially eligible enrollees, defined as pregnant women between 18-45 years old who are capable of providing informed consent, call a toll-free number (1-866-961-2388), or complete an online interest form located on the Registry's website. Women who have been exposed to an atypical antipsychotic during pregnancy are considered cases; controls are those women who have not been exposed to these agents or any other known teratogen since becoming pregnant. Verbal consent from cases and controls is obtained for three phone interviews conducted at the following times: (1) baseline, proximate to the time of enrollment, (2) 7 months gestation, and (3) 2-3 months postpartum. Medical record release authorization is obtained after the 7 month interview for obstetric, labor and delivery, and the newborn pediatric medical records. A trained research assistant blinded to medication exposure reviews the records to abstract relevant information regarding primary and secondary outcomes including: 1) rates of major malformations in infants, and 2) birth weight, gestational age at delivery, miscarriage rates, method of delivery, and delivery complications. Data on maternal health outcomes including weight gain across pregnancy, and gestational hypertension/diabetes are also obtained. Potential major malformations are identified and relevant records are sent to a dysmorphologist blinded to drug exposure for adjudication. Study progress is overseen by a Scientific Advisory Board whose members review interim findings and who determine criteria for Registry findings.

**Results:** As of February 2013, total enrollment in the Registry was 323 women: 235 prospective cases and 88 prospective controls. The overall rate of subjects dropped among cases and controls was 10%. The proportion of study subjects for whom medical records were obtained was 91%. Concordance between the final postpartum interview and information abstracted from medical records regarding the primary outcome variable is high.

**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 critical 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 risks for major malformations in infants is anticipated in the next 12-24 months.

### Learning Objectives:

- Describe goal of National Pregnancy Registry for Atypical Antipsychotics (NPRAA)
- Describe methods of NPRAA

### Source of Funding:

Pfizer (2009-2011), AstraZeneca (current), Bristol-Myers Squibb (current), Sunovion (current), and Ortho-McNeil-Janssen (current)

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## **DOUBLE BLIND PLACEBO CONTROLLED PILOT STUDY OF ADJUNCTIVE QUETIAPINE SR IN THE TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER (PMDD)**

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**Background:** Premenstrual Dysphoric Disorder (PMDD) is a mood disorder consisting of serious premenstrual distress with associated deterioration in functioning. It impacts 5-9% of women (Epperson et al, 2012). PMDD results in the same functional impairment that is observed in major depression and causes decreased quality of life, increased suicide rates, and increased health care utilization. Although the selective serotonin reuptake inhibitors (SSRI's) have become the first line treatment for PMDD, up to 50% or more of women do not have adequate remission of symptoms with SSRI treatment (Pearlstein et al, 2005).

**Objective:** We conducted a prospective diagnostic assessment of PMDD by daily diary ratings in women who had an incomplete response to treatment with an SSRI and enrolled in a double blind placebo controlled study of adjunctive quetiapine SR during the luteal phase.

**Methods:** The study was designed and powered to enroll 50 women with histories of PMDD taking an SSRI or SNRI antidepressant with incomplete response for randomization to adjunctive treatment with quetiapine versus placebo. Fifty-two women completed the baseline assessment that included a structured psychiatric interview. After the baseline visit, the women completed two-months of prospective monitoring by tracking daily symptoms on the Prospective Record of the Impact and Severity of Premenstrual Symptoms (PRISM) calendar, (Reid, 1985). A PMDD diagnosis was made by evaluating the daily PRISM calendar by an independent reviewer. Those meeting strict DSM-IV criteria for luteal phase mood symptoms were randomized to the treatment phase. The dose of the SSRI or SNRI was required to remain unchanged during the study. Starting dose of the study medication (quetiapine SR or placebo) was begun at 25mg and titrated upward for three months of treatment during the luteal phase. Subjects had weekly visits during the luteal phase and dose escalation was determined based on report of ongoing symptoms. Outcome variables included the Hamilton Depression and Anxiety Scales, Clinical Global Impression Scale (CGI) and Prospective Record of the Impact and Severity of Premenstrual Symptoms (PRISM) calendar, (Reid, 1985).

**Results:** Twenty women were enrolled in the treatment phase (N=10 women in the active treatment group (quetiapine SR) and N=10 women in the placebo group). Recruitment was challenging due to the ready availability of quetiapine outside of the study and many women dropped after completing the baseline assessment. The study was underpowered but greater reductions (nonsignificant) in measures of luteal phase mood ratings at the final treatment visit were observed in the adjunctive quetiapine treatment group as compared to the placebo group on the 17-item Ham-D, CGI-improvement rating (2.2 in the active group versus 3.2 in the placebo group) and PRISM score of daily symptoms.

**Conclusion:** PMDD is a serious mood disorder causing significant impairment in functioning. This small double-blind study suggests that adjunctive treatment with quetiapine SR may be a useful addition to first-line SSRI therapy in women with PMDD and may help to target the refractory PMDD symptoms of insomnia, anxiety and irritability. Future research with a larger sample size is needed.

### **Learning Objectives:**

- To examine the efficacy of a novel adjunctive treatment (quetiapine SR) for PMDD in women with refractory mood symptoms to standard therapy

- To explore clinical characteristics and treatment response of luteal phase mood symptoms in women with PMDD treated with adjunctive therapy

**Source of Funding:** Research Grant from Astra Zeneca

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**INITIAL 2-WEEK OUTCOMES FOLLOWING 2 METHODS OF SWITCHING TO ILOPERIDONE FROM RISPERIDONE, OLANZAPINE, OR ARIPIPRAZOLE IN PATIENTS WITH SCHIZOPHRENIA**

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<sup>4</sup>Novartis Pharmaceuticals Corporation

**Background:** Changing (switching) antipsychotics is a common therapeutic strategy when a patient's current antipsychotic has limited efficacy/tolerability.<sup>1</sup> We focus on the results observed within the first 2 weeks following a switch to iloperidone. These results are from a 12-week, randomized, multicenter, open-label trial evaluating 2 approaches (gradual versus immediate) to switching to iloperidone in adults with schizophrenia exhibiting efficacy and/or tolerability problems with risperidone, olanzapine, or aripiprazole.

**Methods:** Patients (aged 18–64 y) diagnosed with schizophrenia and experiencing inadequate efficacy and/or poor tolerability on risperidone, olanzapine, or aripiprazole were randomized 1:1 to gradually switch (ie, dose reductions over the first 2 weeks [to 50% on Day 1, 25% by Week 1, 0% by Week 2]: “GRADUAL”) or immediately switch (ie, immediate discontinuation of current treatment at baseline: “IMMEDIATE”) to open-label iloperidone. Patients were titrated over 4 days to iloperidone 6 mg BID, followed by increases ( $\leq 4$  mg/d) up to 12 mg BID, if needed. Primary variable was the Integrated Clinical Global Impression of Change (I-CGI-C), rated from 1 (improvement) to 7 (worsening).<sup>2</sup> Primary analysis time point was at Week 12.

**Results:** Of the 500 randomized patients (GRADUAL: 240; IMMEDIATE: 260), 175 switched from risperidone, 155 from olanzapine, and 170 from aripiprazole. Over the first 2 weeks of iloperidone treatment, discontinuations for any reason occurred in 8.7% of patients in the GRADUAL group and 10.0% in the IMMEDIATE group. Discontinuations due to treatment-emergent adverse events (TEAEs) were higher in Week 1 vs. Week 2 in the GRADUAL group (4.6% to 0.9%) and the IMMEDIATE group (6.9% to 4.0%).

Incidence of spontaneously reported TEAEs was higher during Week 1 vs. Week 2 for both groups (GRADUAL: 46.7% to 26.4%; IMMEDIATE: 52.3% to 29.7%). Incidence of dizziness, the most common TEAE associated with iloperidone switch, was lower in the GRADUAL (8.8%) vs. the IMMEDIATE (14.2%) group during Week 1; at Week 2, both switch groups demonstrated a decline from Week 1 rates (GRADUAL: 1.3%; IMMEDIATE: 3.2%). In addition, I-CGI-C scores improved for both GRADUAL and IMMEDIATE groups over the first 2 weeks: percentages of patients with a rating of much or very much improved (ie, responders) were 5.4% (Week 1) and 17.5% (Week 2) in the GRADUAL group and 11.1% (Week 1) and 26.1% (Week 2) in the IMMEDIATE group.

**Conclusion:** Switching from risperidone, olanzapine, or aripiprazole to iloperidone either gradually or immediately demonstrated subtle clinical differences regarding clinical response within the first 2 weeks

of therapy. Whereas a gradual-switch (ie, cross-titration) revealed lower initial rates of dizziness, an immediate-switch appeared to yield a higher percentage of responders within the first 2 weeks.

**Learning Objectives:**

- Describe early (Weeks 1 and 2) clinical outcomes after switching from aripiprazole to iloperidone
- Describe differences between gradual and immediate switching to iloperidone.
- 1. Describe early (Weeks 1 and 2) clinical outcomes after switching from risperidone, olanzapine, or aripiprazole to iloperidone.

**Source of Funding:** Study funded by Novartis Pharmaceuticals Corp.

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- 2. Describe differences between gradual and immediate switching to iloperidone.

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**EFFICACY OF SUBCUTANEOUS BREMELANOTIDE SELF-ADMINISTERED AT HOME BY PREMENOPAUSAL WOMEN WITH FEMALE SEXUAL DYSFUNCTION: A PLACEBO-CONTROLLED DOSE-RANGING STUDY**

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**Introduction:** Female sexual dysfunctions (FSDs) are common, distressing conditions for which no drug therapy is currently approved. Bremelanotide is a novel cyclic melanocortin peptide that acts as a melanocortin-receptor-4 agonist presumably modulating brain pathways involved in sexual response. For example, melanocortinergic neurons may stimulate incertohypothalamic dopamine release in the medial preoptic area, a locus implicated in the sexual behavior of both sexes of several species. The present clinical study assessed bremelanotide at 3 double-blind (DB) dose levels vs placebo, as self-administered subcutaneously (SC) on an at-home, as-needed basis by premenopausal women with FSDs.

**Methods:** All subjects had hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), or both disorders, diagnosed by validated instruments. After screening, they received a single-blind, in-clinic placebo dose, followed by 4 weeks of placebo self-dosing. Subjects were then randomized to DB placebo or bremelanotide 0.75, 1.25, or 1.75 mg. The DB treatment comprised 2 in-clinic study-drug doses a week apart, followed by 12 weeks of at-home self-dosing.

**Main outcome measures:** The primary endpoint was change from DB baseline to end of study (EOS) in the number of satisfying sexual events (SSEs) during the 28 days preceding these time points, as recorded by item 10 of the Female Sexual Encounter Profile–Revised. The key secondary endpoints were change from DB baseline to EOS on the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO).

**Results:** Of 1,142 screened subjects, 397 were randomized and 327 completed 1 month of DB study-drug use at home. From DB baseline to EOS, mean (SD) increase in SSEs was 0.2 (2.3) for placebo vs 0.7 (1.8) for 1.25 mg ( $p = 0.0807$ , Van Elteren test) and 0.8 (2.9) for 1.75 mg ( $p = 0.0215$ ). Mean change in FSFI total score was 1.88 (5.92) for placebo vs 2.75 (5.70) for 1.25 mg ( $p = 0.0279$ ) and 4.36 (5.58) for 1.75 mg ( $p = 0.0021$ ). Mean change in FSDS-DAO total score was  $-6.8$  (13.6) for placebo vs  $-9.2$  (10.8) for 1.25 mg ( $p = 0.0508$ ) and  $-13.1$  (12.9) for 1.75 mg ( $p = 0.0005$ ). On all 3 key endpoints, statistical significance or a clinically significant trend vs placebo was also observed in the HSDD-only

and HSDD/FSAD subgroups at 1.25 mg, 1.75 mg, and 1.25/1.75 mg pooled. At all bremelanotide dosages, the most common adverse events were nausea, flushing, and headache, with no marked dosage-dependence.

**Conclusions:** In premenopausal women, bremelanotide self-administered at 1.25 and 1.75 mg SC was effective across all key endpoints. Efficacy was seen in both HSDD and mixed HSDD/FSAD populations. Bremelanotide was also safe and well tolerated. The efficacy findings are consistent with preclinical evidence of bremelanotide mechanisms including indirect monoaminergic effects on sexual function.

**Learning Objectives:**

- On reviewing this poster, the participant should gain (1) an enhanced appreciation of the pathophysiology and presentation of FSDs, and
- An understanding of the efficacy, safety, and potential dosage of bremelanotide self-administered to treat HSDD and FSAD.

**Source of Funding:** Palatin Technologies, Inc.

**Literature References:**

- Diamond LE et al. J Sex Med. 2006;3:628-38.
- Pfaus J et al. J Sex Med. 2007;4(Suppl 4):269-79.

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**PREFRONTAL CORTICAL-STRIATAL HIPPOCAMPAL DYSFUNCTION MEASURED ON THE RADIAL-ARM MAZE IS PREDICTIVE OF COCAINE SENSITIZATION IN RATS WITH NEONATAL VENTRAL HIPPOCAMPAL LESIONS**

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<sup>1</sup>Indiana University School of Medicine

**Background:** Substance use disorder comorbidity in schizophrenia may reflect dysfunctional cortical-striatal circuitry involving glutamatergic derangements implicated in both addictions and schizophrenia. Rats with neonatal ventral hippocampal lesions (NVHL)--a neurodevelopment animal model of schizophrenia--demonstrate post-adolescent onset of schizophrenia-like symptoms including cognitive deficits and increased addiction vulnerability. This preclinical approach sought out: 1) to understand the relationship between cognitive dysfunction and cocaine addiction vulnerability in the NVHL model and 2) to test whether treatment with N-acetyl cysteine (NAC)--a novel glutamatergic modulating agent--can alter one or more of these dual diagnosis measures.

**Method:** Adolescent NVHLs vs. SHAM-operated rats (N=80) were randomized to receive NAC vs. saline injections until the start of RAM testing. Subsequently, all groups underwent cocaine sensitization, followed by discontinuation of injections and a cocaine challenge 2 weeks later.

**Results:** NVHL profiles in RAM performance were characterized by overall deficits in entries-to-repeat (ETR) and over-consumption of the food reward (FL). NAC treatment had no main effect or interaction with NVHLs on these variables. NVHLs showed enhanced short- and long-term cocaine sensitization. Significant and increasingly tight predictive correlations were observed between RAM performance (RATFLETR) and subsequent cocaine sensitization.

**Conclusions:** This study identifies NVHL-based cognitive deficits indicative of cortical-striatal-hippocampal network disconnection in an animal model of schizophrenia. This endophenotype is not substantially altered by NAC treatment but is predictive of subsequent abnormal increases in cocaine sensitization, affirming the importance of this neural network in the pathogenesis of addiction vulnerability in mental illness, suggestive of clinical performance measures of dual diagnosis vulnerability in humans.

**Learning Objectives:**

- To understand the relationship between cognitive dysfunction as measured on the Radial-Arm Maze and vulnerability to the long-term neuroadaptive effects of cocaine in behavioral sensitization in a neurodevelopmental animal model of schizophrenia
- To test whether N-Acetyl cysteine treatment can alter one or more of these dual diagnosis measures



**Source of Funding:** Tseng KY, Chambers RA, Lipska BK. The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. Behavioural brain research. 2009;204(2):295-305.

**Literature References:**

- Baker DA, McFarland K, Lake RW, Shen H, Toda S, Kalivas PW. N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. Annals of the New York Academy of Sciences. 2003;1003:349-51.

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**HYPOMETHYLATION IN FEMALE BIPOLAR PATIENTS WITH METABOLIC SYNDROME TAKING OLANZAPINE AND CLOZAPINE**

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**Objectives:** Increasing rates of metabolic syndrome in bipolar disorder has led to the identification of potential risk factors such as atypical antipsychotic use, gender and pharmacogenetics.

Pharmacoepigenetics aims to discover how genes interact with medications and global methylation status is a potential biomarker that may represent genomic stability. Data has linked metabolic syndrome status, gender and antipsychotic type as having effects on global methylation status in the schizophrenia population however, to date, this has not been investigated in bipolar disorder. This pilot study aimed to identify the effect of metabolic syndrome on global methylation status in patients diagnosed with bipolar disorder.

**Methods:** Associations between global methylation (measured by the LUMInometric assay) and metabolic syndrome was assessed in a cross sectional cohort of bipolar patients undergoing a clinical assessment for metabolic syndrome (NCEP\_ATP\_IIIa). Antipsychotic use was broken down based on known risk to cause metabolic side effects with group 1 containing olanzapine and clozapine users, group 2 containing risperidone, quetiapine and paliperidone users and group 3 containing ziprasidone, aripiprazole and any typical antipsychotic users. Regression analysis was conducted after stratifying subjects by metabolic syndrome to investigate the effect of metabolic syndrome, antipsychotic type and gender on methylation status.

**Results:** The study included 82 subjects with a mean age of 43±11.9 years. The cohort was 70% female, 83% Caucasian and 40% met metabolic syndrome criteria. Nine percent were in antipsychotic group 1, 36% in group 2 and 55% were in group 3. In bipolar subjects *without* metabolic syndrome global methylation was not associated with gender, antipsychotic group or metabolic syndrome (whole model p=0.4, average methylation 73%). However, when looking at bipolar subjects *meeting* metabolic syndrome criteria, the whole model was significant (p=0.01). Overall, there was a significant gender, medication interaction where females taking olanzapine or clozapine had significantly lower global methylation levels versus females taking other antipsychotics and males taking any antipsychotic (46.4% methylation vs. 73% for all others).

**Conclusion:** Our results suggest that female bipolar patients taking antipsychotics may have the greatest risk for metabolic side effects potentially due to significantly lower methylation levels and thus lower genomic stability. These findings may begin to elucidate the underpinnings of known differences in gender and antipsychotic propensities to cause metabolic syndrome within bipolar disorder. This global hypomethylation in females may be used to identify those at greatest risk for metabolic syndrome when treating with an antipsychotic as well as being used as a target for metabolic syndrome treatment with methyl donors.

**Learning Objectives:**

- Understand the folate cycle's role in epigenetics and metabolic syndrome
- Interpret the findings from this pilot study and how it applies to bipolar treatment with antipsychotics
- 3. Evaluate the impact of epigenetics on mental health treatment as well as the potential limitations

**Source of Funding:** This project was supported by the NIMH (R01 MH082784), NIH-NCCR, GCRC Program (UL1RR024986), the Chemistry Core of the Michigan Diabetes Research and Training Center (NIH5P60 DK 20572), and the Washtenaw Community Health Organization (WCHO), The National Alliance for Research in Schizophrenia and Depression (NARSAD, ), and the Prechter Longitudinal Study of Bipolar Disorder .

**Literature References:**

- Burghardt KJ, Ellingrod VL. Detection of Metabolic Syndrome in Schizophrenia and Implications for Antipsychotic Therapy: Is There a Role for Folate? *Mol Diagn Ther*. 2013 Jan 23. [Epub ahead of print] PMID: 23341251 [PubMed - as supplied by publisher]
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- Sant KE, Nahar MS, Dolinoy DC. DNA methylation screening and analysis. *Methods Mol Biol*. 2012;889:385-406.

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**THE IMPACT OF CONTINUOUS VERSUS INTERMITTENT HIGH FREQUENCY STIMULATION OF THE NUCLEUS ACCUMBENS ON ETHANOL PREFERENCE AND CIRCADIAN LOCOMOTOR ACTIVITY IN ALCOHOL PREFERRING RATS**

Osama Abulseoud, MD<sup>1</sup>, Christina Ruby, Rajas Kale, Ahmed Ahmed, Susannah J. Tye, BSc (Hon I), Ph.D.<sup>1</sup>, Abbas Kouzani, Kendall Lee, Mark A. Frye, M.D.<sup>1</sup>, Doo-Sup Choi

<sup>1</sup>Mayo Clinic

**Background:** Emerging evidence documents the efficacy of high frequency stimulation of the nucleus accumbens (NAc) in reducing ethanol consumption in cases with refractory alcohol dependence. This study aimed to investigate the effect of different patterns of high frequency stimulation at the nucleus accumbens shell on ethanol preference and circadian locomotor activity in adult male alcohol preferring (P) and non-preferring (NP) rats.

**Methods:** High frequency stimulation (amp=1V, frequency=130Hz, pulse width= 0.1 ms) ) in the shell of the right NAc (Coordinates from bregma: AP=+2.0 mm, ML= ± 1.2 mm, DV= -6.5 mm from dura) was initiated at one of three stimulation patterns: (1) Continuous stimulation for 7 days using a small battery powered device (n=7), (2) intermittent stimulation for 4 hours initiated at the beginning of the light phase (n=6), or (3) intermittent stimulation for 4 hours initiated at the beginning of the dark phase using the MINCS device (n=6). Ethanol and water intake were monitored for at least a week after stimulation. Circadian locomotor activity counts in home cage were recorded using an infrared motion detector interfaced with a computerized data acquisition system (Clocklab) and later analyzed using MatLab software.

**Results:** Continuous stimulation of the NAc reduced ethanol consumption and preference in P rats (table 1), with little effect on either parameter in NP rats. In contrast, NAc stimulation only during the dark phase or light phase induced circadian arrhythmia in P rats with a concomitant increase in ethanol intake noted during nighttime stimulation

Stimulation pattern	Pre Stimulation	Stimulation ON	Post Stimulation	One-way ANOVA (P value)

Light-phase	17.36±2.558	25.16±1.794	24.07±2.170	0.0397
Dark-phase	16.06±0.8529	25.82±3.112	21.13±3.511	0.0506
Continuous	27.26±1.103	<b>19.52±2.804</b>	22.97±1.361	0.0369

**Conclusions:** These results suggest that alignment of circadian rhythms by continuous NAc stimulation may play a role in reducing drinking in alcohol preferring rodents.

**Learning Objectives:**

- To investigate the effect of high frequency nucleus accumbens stimulation pattern on ethanol drinking in rats
- To examine if circadian rhythm regulation mediates the effect of accumbens deep brain stimulation on reducing ethanol preference

**Source of Funding:** *NIH/NCRR CTSA KL2 to Dr. Abulseoud (RR024151)*

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# Thursday, May 30, 2013

## Poster Session 2

### Regency Ballroom

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#### **DEVELOPING TREATMENTS FOR SCHIZOPHRENIA AND CO-OCCURRING SUBSTANCE USE DISORDER: TARGETING BRAIN REWARD CIRCUITRY**

Alan Ivan. Green, MD<sup>1</sup>, Adina S. Fischer, B.Sc., M.D.-Ph.D. Candidate<sup>2</sup>, Robert Roth, PhD<sup>3</sup>, Susan Whitfield-Gabrieli, ABD/PhD<sup>4</sup>, Danielle Gulick, PhD<sup>5</sup>, Mary Brunette, M.D. <sup>3</sup>

<sup>1</sup>Geisel School of Medicine at Dartmouth, <sup>2</sup>Dartmouth Medical School, <sup>3</sup>Department of Psychiatry, Geisel School of Medicine at Dartmouth, <sup>4</sup>MIT, <sup>5</sup>University of South Florida Health

Substance use disorder (especially involving alcohol or cannabis) occurs commonly in patients with schizophrenia and worsens their overall outcome. Treatment approaches that limit co-occurring substance use in these patients are limited. Most antipsychotic medications tested do not limit such substance use. Retrospective, open label, and recent small N randomized trials by our group and others all suggest, however, that the atypical antipsychotic medication clozapine does, in fact, limit both alcohol and cannabis use in these patients. Unfortunately, the side effects of clozapine have severely restricted its clinical use. We have proposed that a dysfunctional dopamine mediated brain reward circuit in patients with schizophrenia may underlie their substance use, and, further, that substance use may ameliorate this dysfunction while also worsening symptoms of schizophrenia. Moreover, we have further proposed that clozapine, through its weak dopamine D2 receptor blockade, coupled with its effects on the noradrenergic system, may also tend to ameliorate this brain reward circuit dysfunction. Studies of resting state connectivity with fMRI, as well as task-based fMRI, in patients with schizophrenia and co-occurring cannabis use disorder are consistent with the reward dysfunction hypothesis in these patients. Moreover, pilot data suggest that cannabis may modulate this dysfunction. In studies of alcohol-drinking rodents, use of medication combinations to mimic the pharmacological action of clozapine suggest possible pathways toward development of new treatments for schizophrenia that may limit their substance use. Data from these animal and human studies will be presented, which taken together, provide intriguing clues about the basis of co-occurring substance use disorder in patients with schizophrenia and possible pathways toward developing effective treatments.

#### **Learning Objectives:**

- To review use of antipsychotic medication in patients with schizophrenia and substance use disorder.
- To propose a strategy for developing new treatment for schizophrenia and substance use disorder that targets a dysfunctional brain reward circuit.

**Source of Funding:** Grant funding from NIAAA: R03AA014644; R01AA11904; R01AA018151; R21AA019534.

Grant funding from NIDA: R01DA026799; R21DA019215; R01DA032533; R01DA13196

#### **Literature References:**

- Brunette MF, Dawson R, O'Keefe CD, Narasimhan M, Noordsy DL, Wojcik J, Green AI. A randomized trial of clozapine vs. other antipsychotics for cannabis use disorder in patients with schizophrenia. *Journal of Dual Diagnosis*, 2011: 7(1-2): 50-63.
- Chau DT, Ahmed J, Wang TT, Xie H, Dawson R, Green AI. Risperidone lessens the ability of clozapine to suppress alcohol drinking in Syrian golden hamsters. *Neuropharmacology*, 2011: 61(4): 646-652.

## **MINDFULNESS MEDITATION FOR ALCOHOL RELAPSE PREVENTION: FINDINGS FROM A RANDOMIZED CONTROLLED TRIAL**

Aleksandra Zgierska, MD, PhD<sup>1</sup>

<sup>1</sup>University of Wisconsin, School of Medicine & Public Health, Department of Family Medicine

**Background:** Relapse prevention is one of the most challenging issues in the treatment of alcohol dependence. Mindfulness meditation, a popular mind-body therapy, is a promising treatment for substance use disorders. However, there are no rigorous studies evaluating the effects of mindfulness-based interventions in alcohol dependence.

**Goal:** To evaluate effects of mindfulness-based intervention on alcohol consumptions and drinking-related negative consequences among adult recovering alcoholics.

**DESIGN:** Two-arm, partially-blinded (data analysis) randomized (1:1) controlled trial (RCT) with 52-week follow-up; results from preliminary analyses of 26-week follow-up are reported.

**Methods:** Participants: Adult alcoholics who quit drinking 2-14 weeks prior to enrollment and participated in outpatient behavioral addiction treatment for at least 2 weeks.

**Intervention:** Eight-week long meditation intervention (mindfulness based relapse prevention + standard of care (SOC) for alcohol dependence) or wait-list control (SOC only).

**Outcomes:** Self-reported at 0, 8 and 26 weeks. Primary outcomes: alcohol consumption (standard drinks; Timeline Followback Method) from 12 weeks prior to alcohol-quit date through follow-up. Secondary outcome: severity of drinking-related harms (Drinker Inventory of Consequences), past 3 months.

**Results:** Of 292 screened, 123 were enrolled (64 meditation, 59 control group). No baseline differences were noted between the groups ( $p \geq 0.05$ ). Participants were on average  $41.2 \pm \text{SD } 12$  years old, 56% male and 90% white. About half were married, employed and earning  $\geq \$20,000/\text{year}$ , with 84% reporting at least some college education. About half reported hospital or residential, and one-third at least 3 outpatient treatments for alcoholism. During the 12 weeks prior to quit date, they consumed on average  $511 \pm 423$  drinks, drinking on  $60 \pm 38\%$  of days, and drinking heavily on  $51 \pm 35\%$  of days.

Over the 26-week study period, the retention rate was 93%; 103 provided follow-up data and were included in the Generalized Linear Mixed Model analysis. No statistically significant differences were noted between the groups in drinking outcomes: % drinking days, % heavy drinking days, total number of drinks or drinks-per-day. However, the meditation group reported lesser severity of drinking-related harms ( $p=0.043$ ). No important adverse events or side effects were noted.

**Conclusions:** These preliminary findings indicate that mindfulness based intervention for alcohol relapse prevention may not affect alcohol consumption but may decrease drinking-related negative consequences suggesting improved coping skills among participants in the meditation group.

ClinicalTrials.gov #: NCT01056484

### **Learning Objectives:**

- To identify the potential application of mindfulness based interventions as treatment for substance use disorders.
- To explore possible implications of the study findings for clinical practice and future research.

### **Source of Funding:**

NIH NIAAA K23 AA017508

### **Literature References:**

- Zgierska A, Rabago D, Chawla N, Kushner K, Kohler R, Marlatt A. Mindfulness meditation for substance use disorders: A systematic review. *Substance Abuse* 2009; 30:266-294. PMID: PMC2800788
- Zgierska A, Rabago D, Zuelsdorff M, Miller M, Coe C, Fleming MF. Mindfulness meditation for relapse prevention in alcohol dependence: A feasibility pilot study. *Journal of Addiction Medicine* 2008; 2(3):165-173.

Lori A. Knackstedt, PhD<sup>1</sup>

<sup>1</sup>University of Florida, Psychology Dept.

Alcohol addiction is a substantial public health problem in the United States today. A high risk of relapse exists despite long periods of abstinence, and this relapse can be modeled in animals using the extinction-reinstatement paradigm. This paradigm involves training animals to respond for alcohol reinforcement in a standard two-lever operant chamber. The operant response is then extinguished and reinstated with cues previously paired with the response made to attain alcohol delivery, or the pharmacological stressor, yohimbine. We propose that glutamate homeostasis is altered after alcohol administration. We tested whether restoring homeostasis with the nutritional supplement N-acetylcysteine or the antibiotic Ceftriaxone can attenuate cue- and yohimbine-primed reinstatement. Rats were trained to drink a solution with a high concentration of ethanol (20% v/v) using 12 overnight 24-hour drinking bouts which were each followed by 24 hours of no alcohol access. This phase was followed by daily 45-min operant self-administration sessions for 26 sessions (5 sessions/week) during which animals responded on an FR-3 schedule and discrete cues were paired with delivery of the alcohol solution into the dipper tray. Our results show that modulating glutamate levels with NAC attenuates yohimbine-primed reinstatement, but not cue-primed reinstatement. Ceftriaxone decreased both cue- and yohimbine-primed reinstatement, however this effect was likely due to the gastrointestinal side-effects of this compound as control animals treated with an antibiotic not known to affect glutamate also decreased alcohol-seeking. These results indicate that N-acetylcysteine reduces stress-induced relapse to alcohol and may warrant testing in human alcoholics.

**Learning Objectives:**

- To identify the changes in the glutamate transmitter system that occur following long-term alcohol consumption in rodents
- To learn about medications which counteract glutamate alterations following alcohol and whether those medications can prevent alcohol relapse

**Source of Funding:** Medical University of South Carolina's Alcohol Research Center Pilot Award

**Literature References:**

- Larowe et al., *Am J Psychiatry*. 2007 Jul;164(7):1115-7.
- Mardikian et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007 Mar 30;31(2):389-94.

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**THE SEROTONIN-PREFERRING TRIPLE REUPTAKE INHIBITOR AMITIFADINE DECREASES ALCOHOL INTAKE AND IMPULSIVITY IN RODENTS**

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<sup>1</sup>Euthymics Bioscience, Inc., <sup>2</sup>Euthymics Bioscience Inc., <sup>3</sup>National Institute on Alcohol Abuse and Alcoholism/National Institutes of Health/Department of Health and Human Services, <sup>4</sup>Medical University of South Carolina, <sup>5</sup>Indiana University School of Medicine, Department of Psychiatry, Institute of Psychiatric Research, <sup>6</sup>Dept. of Psychology, IUPUI, <sup>7</sup>Indiana University School of Medicine, <sup>8</sup>Medical University Of South Carolina

**Introduction and Objective:** Alcohol (ALC) Use Disorder (AUD) is a chronic, relapsing medical disorder afflicting 18 million persons in the U.S., and ranks 5th and 3rd, respectively, on the WHO list of preventable causes of morbidity and mortality. Dopamine (DA) and serotonin (5-HT) circuitry underlie neurobehavioral domains relevant to alcoholism, including reinforcement, craving, and mood. The 5-HT-preferring triple reuptake inhibitor amitifadine (AMI) has been shown in an operant model to reduce ALC intake, but not sucrose intake, in ALC-preferring (P) rats, and also reduce withdrawal-induced anhedonia and depressive-like behaviors (Warnock et al., 2012). Here we report the effects of AMI in several other accepted genetic rodent models of free choice ALC intake as well as impulsivity - a key component of addiction.

**Methods:** Free choice ALC intake during a 2 hr period was determined in the P rat model of binge drinking and the high-ALC drinking (HAD) rat model of heavy drinking for 5 days, and after a 2 week withdrawal/relapse period. The effects of AMI on drinking in C57BL/6J mice made ALC-dependent by exposure to ALC vapors were also evaluated. Impulsivity in high-ALC preferring (HAP) mice was determined using an adjusting amount delay discounting (DD) task employing 2 levers to present a choice between small-immediate versus large-delayed saccharin rewards to estimate the subjective value of the delayed reinforcer.

**Results:** In both P and HAD rats in a dose-dependent manner, AMI 1) significantly decreased ALC intake during a 2 hr limited ALC access period over 5 consecutive days; and 2) decreased ALC intake in a relapse test following a 2-week withdrawal period. AMI significantly increased water intake in P rats at several doses, and decreased 24 hr food intake at the highest dose in both strains, but with no changes in body weight. In the ethanol dependence and relapse drinking mouse model, AMI significantly reduced escalated voluntary ALC intake in dependent mice and to a lesser extent, stable intake in non-dependent mice. In the highly impulsive HAP mice, AMI increased the mean adjusted value and total saccharin intake (i.e., reduced impulsivity). AMI also dose-dependently reduced 12 hour ALC consumption in the HAP mice.

**Conclusion:** AMI dose-dependently and significantly reduced acute and sub-chronic free choice ALC consumption for up to 5 days in the P and HAD models of AUD as well as after a withdrawal/relapse period. AMI had modest effects on food and water intake but did not alter body weight, suggesting little or no effect on general consummatory behaviors. In mice rendered dependent via ethanol vapor exposure, AMI had a greater effect in ALC-dependent mice than non-dependent mice, suggesting a specific effect on excessive levels of drinking associated with dependence. In HAP mice, AMI reduced ALC intake and impulsivity. The minimal effective dose (MED) required to decrease ALC consumption and impulsivity was about twice the MED in rodent depression models. The combined effects of reductions in ALC intake, impulsivity, and withdrawal-induced behaviors suggest that amitifadine could be efficacious for treatment of AUD, perhaps via modulation of 5-HT and DA neurotransmission.

**Learning Objectives:**

- To become familiar with genetic rodent models of alcoholism and impulsivity that can identify potential new treatments for alcoholism
- To become familiar with results in these models suggesting amitifadine may be effective for the treatment of alcoholism

**Source of Funding:** Euthymics Bioscience, Inc. is supported by venture capital funding.

The studies in this abstract were supported by NIH grants HHSN262700700037C and HHSN262700700038C

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**A HUMAN ALCOHOL SELF-ADMINISTRATION PARADIGM TO MODEL INDIVIDUAL DIFFERENCES IN IMPAIRED CONTROL OVER ALCOHOL USE: INITIAL AND SECONDARY FINDINGS**

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We developed a self-administration paradigm to model impaired control over alcohol use (i.e., diminished ability to avoid alcohol use altogether or to control use once initial consumption has begun). Impaired control is an early indicator of problem drinking (Leeman et al. 2012), making a laboratory model of the construct a valuable research tool. Young adult heavy drinking is a public health concern for which there are few efficacious interventions. Novel interventions for this population could be tested efficiently on a preliminary basis using laboratory paradigms such as this one.

The impaired control laboratory paradigm includes moderate drinking guidelines meant to model limits on alcohol consumption, which are typically exceeded by people with impaired control. Possible payment reductions created a disincentive for excessive drinking and modeled negative consequences of alcohol use. Self-administration of alcohol above the guideline, despite possible pay reduction was considered indicative of impaired control and is potentially indicative of current problem drinking and risk for more serious problems subsequently.

Heavy-drinking young adults ( $N = 39$ ) self-administered beers *ad libitum* in a bar setting for 3 hours with 1-3 other participants, in order to account for relevant social factors motivating young adult alcohol consumption. Participants were randomized to a condition containing the laboratory paradigm's key components or a free drinking condition missing these components.

Experimental condition participants self-administered significantly fewer beers and drank to significantly lower blood-alcohol concentrations (BACs) than those in the free-drinking condition. At the same time, there was a broad range of response in the experimental condition (BAC range = .024-.097) and several participants drank excessively despite the provision of moderate drinking guidelines and possible pay reductions. The ability to elicit a broad range of responses is a key feature of self-administration paradigms, as such variability is necessary to observe effects of pharmacotherapy and other experimental manipulations.

These results, which have been reported previously, will be included to provide background on the impaired control laboratory paradigm. The following new results will also be presented. Alcohol self-administration in the experimental condition was related to problem drinking risk variables including early age of alcohol use onset. Also, those who self-reported needing a higher number of drinks to experience subjective effects in their initial drinking experiences self-administered more beers in the experimental condition. There is evidence supporting low initial subjective response as a risk factor for subsequent alcohol dependence (Trim et al, 2009). Greater *ad libitum* beer consumption in the experimental condition was also related to lower perceived intoxication. These findings suggest relationships between impaired control and low subjective response to alcohol. Testing preliminary efficacy of interventions for heavy drinking young adults with low subjective response is a potential use for the impaired control laboratory paradigm. This and other future directions will be discussed.

#### **Learning Objectives:**

- Understand impaired control as an early indicator of problem alcohol use
- Some of the findings in this abstract have been presented at the Research Society on Alcoholism Annual meeting, June 2012. This abstract also includes new findings that have not yet been presented.

#### **Source of Funding:**

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## **PREDICTORS OF DRINKING OUTCOME DURING FOLLOW-UP IN COMBINE**

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While the focus of most statistical analyses of randomized clinical trials is on between-group comparisons during treatment, it is also important to identify predictors, measured at baseline and during treatment, of longer term outcomes. The goal of the current study was to use tree-based methods<sup>1</sup> to identify good drinking outcomes during the one-year follow-up in COMBINE<sup>2</sup>, the largest study of pharmacotherapy for alcoholism in the United States to date. Tree-based methods have a number of advantages over traditional regression-based methods. They consider a large pool of predictors, empirically identify subgroups of subjects with good outcome based on interactions rather than main effects, and present the results in the form of decision trees that are easily interpreted by clinicians. In the current study we focus on the clinically meaningful outcome of no heavy drinking during the last two months of the one year follow-up in COMBINE and consider over one hundred potential predictors. Individual classification trees and deterministic forests are constructed and interpreted. We demonstrate that drinking outcomes during treatment are the best predictors of longer term good outcome. Specific combinations of drinking outcomes during treatment and baseline predictors are associated with best outcome. Sensitivity analyses based on different methods for treating missing data are also performed. The constructed trees need to be externally validated in other samples. The results emphasize the importance of optimizing treatment outcomes during treatment and identify potential subgroups of subjects who require most extensive monitoring in order to achieve good long-term outcome.

### **Learning Objectives:**

- To understand the value of the tree-based approach over traditional regression methods for predicting outcome.
- To learn what combinations of baseline predictors and drinking outcomes during treatment are associated with good long-term drinking outcomes in COMBINE.

### **Source of Funding:**

This work was supported by the National Institute on Alcohol Abuse and Alcoholism [R01AA017173, K05 AA014715].

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- Anton, R.F., O'Malley, S.S., Ciraulo, D.A., et al., for the COMBINE Study Research Group. (2006). Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence: The COMBINE Study: A Randomized Controlled Trial. JAMA 295:2003-2017.

## **ADVANCED BRAIN IMAGING, PHYSIOLOGY, AND GENETICS FOR CLINICAL TRIALS IN NEUROLOGICAL AND PSYCHIATRIC DISEASE**

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<sup>1</sup>The Mind Research Network

**Background:** Functional brain imaging technologies including functional MRI and magnetoencephalography (MEG) continue to emerge as valuable tools in the differential diagnosis of neurological and psychiatric disorders. In some cases, these methods also provide valid intermediate markers of disease progression and treatment, with data collected at baseline predictive of subsequent treatment response.

**Approach:** As part of our effort to advance pharmaco-imaging, we have acquired a large database of information from control subjects including over 1000 MRI/fMRI scans, and 200+ MEG/EEG evaluations. Data are also available from a number of clinical populations including subjects with Alzheimer's dementia, epilepsy, autism, schizophrenia, depression, traumatic brain injury, and multiple

sclerosis. Using a variety of data analysis methods, including independent component analysis, it is possible to reveal hidden patterns of biomarkers that correlate with disease state and severity.

**Results:** In each of these areas, we have identified imaging-based biomarkers associated with disease state and severity. In several conditions, including autism, depression, and tbi, we have identified markers that track disease progression and treatment response, with some baseline data predictive of final clinical outcome. Examples will be provided in Autism, Alzheimer's Disease, Depression and Traumatic Brain Injury.

**Conclusion:** Multimodal imaging methods can provide novel biomarkers and intermediate treatment endpoints for clinical trials.

**Learning Objectives:**

- To understand the use of brain imaging for differential diagnosis.
- To understand the use of brain imaging for prediction of disease progression or treatment response

**Source of Funding:** NA

**Literature References:**

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**A PROOF OF CONCEPT STUDY OF TOLCAPONE FOR PATHOLOGICAL GAMBLING: RELATIONSHIPS WITH COMT GENOTYPE AND BRAIN ACTIVATION**

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**Rationale:** Pathological gambling (PG) is a disabling disorder experienced by 1%-3% of adults, and empirically validated treatments are lacking. Perturbations of prefrontal-dependent cognitive functions are implicated in the pathophysiology of PG. The enzyme catechol-O-methyl-transferase (COMT) is known to regulate such functions and their neural substrates.

**Objectives:** The objective of this study was to determine whether tolcapone, a COMT inhibitor, improves symptoms of PG and to explore whether such effects are dependent on COMT val-158-met polymorphism status and relate to concomitant changes in fronto-parietal activation. *Methods:* Twenty-four individuals with PG were enrolled in an eight-week trial of tolcapone (100mg/day titrated to 100mg po tid) and twelve undertook pre and post-treatment fMRI to examine brain activation during an executive planning task in a pre-defined fronto-parietal network.

**Results:** Treatment was associated with statistically significant reductions on PG-Yale Brown Obsessive Compulsive Scale (PG-YBOCS), and these benefits were significantly more pronounced in subjects with the val/val COMT polymorphism. Data from the fMRI task identified (i) planning related fronto-parietal under-activation in PG subjects before treatment compared to controls; and (ii) augmentation of planning related fronto-parietal activation following tolcapone treatment. There was also a significant correlation between PG-YBOCS improvement and treatment-related increases in fronto-parietal activation during executive planning.

**Conclusions:** Tolcapone improved PG symptoms, and that the extent of symptomatic improvement was significantly related to COMT status and augmentation of fronto-parietal activation (fMRI probe). Objective genetic and fMRI markers hold promise in the search for targeting treatment and elucidating brain mechanisms associated with optimal clinical outcomes.

**Learning Objectives:**

- Understand potential pharmacological treatment for pathological gambling

- Understand how genetics and neuroimaging may improve treatment options for pathological gambling

**Source of Funding:** Internal funds.

**Literature References:**

- Apud JA, Mattay V, Chen J, Kolachana BS, Callicott JH, Rasetti R et al (2007). Tolcapone improves cognition and cortical information processing in normal human subjects. *Neuropsychopharmacology* 32: 1011-1020.
- Hodgins DC, Stea JN, Grant JE (2011). Gambling disorders. *Lancet* 378: 1874-1884.

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**GENE EXPRESSION PROFILE IN A PRECLINICAL MODEL OF ANTIDEPRESSANT RESISTANCE: TOWARDS A BIOMARKER SIGNATURE**

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**Background:** Stress is implicated in the pathophysiology of mood disorders (McEwen, 1992).

Antidepressants buffer against stress-mediated neurodegeneration and enhance psychological coping. An individual's capacity to cope with stress is fine-tuned through epigenetic regulation of stress-mediated gene transcription (Vialou et al., 2013). Two key brain regions that mediate coping under stress include the infralimbic cortex (IL) and nucleus accumbens (NAc). To investigate the neural adaptations mediating antidepressant resistance, we have quantified the effects of chronic adrenocorticotrophic hormone (ACTH) treatment on tricyclic antidepressant efficacy, monoamine tissue levels and gene expression in the IL and NAc.

**Methods:** Male sprague dawley rats were treated with ACTH (100µg/day i.p.) for 14 days. On treatment days 14 and 15, animals were administered either tricyclic antidepressant (imipramine hydrochloride 10mg/kg i.p.) or control saline (0.9% i.p.) before undergoing the open field test (OFT; day 14) and forced swim test (FST; days 14 & 15). Animals were sacrificed and brains snap frozen in liquid nitrogen 1 hour after exposure to the FST. PFC monoamine levels, together with the IL and NAc transcriptome, were quantified in control and adrenocorticotrophic hormone (ACTH)-treated antidepressant-resistant animals. Genes were determined to have differential gene expression if  $p < 0.05$  following Bonferroni correction for multiple comparisons. Global gene expression profiles (Agilent) were obtained and gene set enrichment analysis performed using the Database for Annotation, Visualization and Integrated Discovery analysis (DAVID).

**Results:** Chronic (14 day) treatment with ACTH (100µg/day i.p.) prevented imipramine (10mg/kg)-mediated reductions in FST immobility, effectively blocking tricyclic antidepressant efficacy. PFC tissue levels of serotonin and norepinephrine were significantly elevated, and dopamine levels attenuated, in ACTH-treated animals post-FST, relative to controls. The gene expression profile indicated insulin signaling, synaptic plasticity, extracellular matrix protein scaffolds, mitochondrial function, immune response and DNA repair were dysregulated in ACTH-treated animals.

**Conclusions:** Chronic ACTH treatment dysregulates monoaminergic systems and elicits a state of tricyclic antidepressant resistance. Changes in gene expression suggest that ACTH treatment has altered cellular responses to FST stress in the IL and NAc. These altered signaling pathways may contribute to the observed antidepressant resistance, and further studies are needed to validate their potential use as a biomarker signature.

**Learning Objectives:**

- Identify etiological factors involved in antidepressant treatment resistance.
- Describe transcriptomic biomarker strategy for individualizing antidepressant treatment.

**Source of Funding:** NARSAD YI Award

**Literature References:**

- McEwen B. Steroid hormones: effect on brain development and function. *Horm Res.* 1992. 37:1–10.
- Vialou V, Feng J, Robison AJ, Nestler EJ. Epigenetic mechanisms of depression and antidepressant action. *Annu Rev Pharmacol Toxicol.* 2013. 53:59-87.

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## **PERSONALIZED RESPONSE INDICATORS OF SSRI EFFECTIVENESS IN MAJOR DEPRESSION (PRISE-MD): USE OF AN EEG-BASED BIOMARKER TO GUIDE TREATMENT SELECTION IN MDD**

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**Specific Purpose:** Care for depression could be improved if the trial-and-error approach of sequential medication choice were enhanced by a biomarker that predicted likelihood of remission for a specific patient to a specific treatment. Previously, an EEG-based biomarker called the Antidepressant Treatment Response (ATR) index used data at baseline and week 1 of treatment, and could usefully differentiate end-of-trial remitters and non-remitters (BRITE-MD trial). The PRISE-MD project was undertaken with prospective stratification using ATR to assess the accuracy of this frontal quantitative EEG (fqEEG) biomarker in predicting outcomes with an SSRI. We hypothesized that treatment consistent with the biomarker prediction would be associated with significantly better outcomes than treatment not consistent with the biomarker.

**Methodology:** 180 adults with DSM-IV-defined major depressive disorder (MDD) began treatment with escitalopram (ESC; 10 mg/d), and after 1 week were assigned either to: 1) continue ESC (10 mg/d) for 7 more weeks; 2) switch to bupropion XL (300 mg/d) for 7 weeks. Stratified randomization used ATR to balance ATR values (high vs low) between treatment groups. Symptom severity was assessed with the 17-item Hamilton Depression Rating Scale (HAM-D) and 4-channel fqEEG was recorded. Remission was defined as final HAM-D $\leq$ 7. The composite EEG index (ATR) from BRITE-MD was used to predict clinical outcome.

**Results:** 73 subjects on ESC were evaluated after excluding protocol violators and subjects with excessive EEG artifact. For them, the remission rate was significantly higher in ATR-consistent group (predicted to do well) than for ATR-inconsistent group (60.4% vs. 30.0%,  $p=0.01$ ). Remitter subjects had significantly higher mean ATR than non-remitters ( $p<0.05$ ).

**Conclusions:** This replication and extension study confirms the use of an EEG-based biomarker at week 1 of ESC treatment to help guide antidepressant selection in MDD. Subjects whose ATR predicts response or remission do better when continued on ESC, while subjects whose ATR predicts poorer outcomes with ESC may benefit from alternate regimens.

### **Learning Objectives:**

- describe recent and current research into physiologic biomarkers that could support a personalized medicine approach to managing depression
- critically consider the next steps needed to support the integration of this paradigm shift into clinical management

**Source of Funding:** R01MH085925 from NIMH; ATR equipment provided by Covidien (Aspect Medical Systems).

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## **DIFFERENTIAL ITEM FUNCTIONING AND THE ALZHEIMER'S DISEASE ASSESSMENT SCALE-COGNITIVE (ADAS-COG)**

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**Background:** The ADAS-Cog is a well-recognized measure of cognitive assessment in patients with Alzheimer's Disease (AD). It has been suggested some items and subscales of the ADAS-Cog may be better measures of cognitive functioning for different stages of AD. Despite the popularity of the ADAS-Cog, few studies have examined its item properties among patients with Mild Cognitive Impairment (MCI) and moderate impairment, and further validation of the ADAS-Cog is needed to substantiate its use at different stages of AD. This study examined whether there are differences in response to a particular item as a function of respondent characteristics (Apolipoprotein E and Impairment level) in the ADAS-Cog.

**Methods:** jMetrik was used to analyse the ADAS-Cog. AD data was obtained from the Critical Path Institute Online Data Repository (CODR). Separate Rasch analyses were conducted comparing ApoE carriers (n = 505) vs non-carriers (n = 507), and MCI (MMSE = 21 to 26; n = 1362) and Moderate impairment (MMSE 14 to 20; n = 1211) to examine summary and individual model fit statistics, person separation index (PSI), response format, local dependency, targeting, item bias (or differential item functioning -DIF), and dimensionality.

**Results:** Based on the results of Rasch analyses different approaches can be taken to account measurement bias in properties of the ADAS-Cog post-hoc. Lower item calibration (Delta) reflects items with bias, indicating whether subgroups respond to items differently. The average age of 74.08 years (SD = 8.15) with 55.7% male patients. Commands (Delta = 0.23), Constant Praxis (0.26), Ideational Praxis (0.32), and Naming Objects (0.26) shows 'moderate' DIF, favoring the Moderately impaired group, indicating that this item functions better in this group. Orientation (Delta = 1.34) shows 'Large' DIF, favoring the Moderately impaired group, indicating that this item functions better in this group. Word Recognition (-1.38) and Word Recall (-1.20) shows 'Large' DIF, favoring the MCI group, indicating that this item functions better in this group.

**Conclusions:** This study looks at a levels of impairment and item summary for the ADAS-Cog. There were significant differences in response to a number of items on the ADAS-Cog, possibly caused by a lack of consistency in testing administration, or scoring parameters of the ADAS-Cog. The choices made during analysis will substantially affect the results, and we have described and illustrated that the subgroups may have different impact on different items affecting outcome.

### **Learning Objectives:**

- A large number of data exists in ADAS-Cog from both Alzheimer's trials and assessing how each item functions as an outcome can provide insights about parts of the scale that may be better suited for MCI and early AD trials
- Understanding how item response analyses can be used to assess the measurement properties of the ADAS-cog across the range of cognitive dysfunction in AD.

**Source of Funding:** ProPhase LLC, New York City, NY

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**MEDICAL COMORBIDITY AND CARDIOVASCULAR RISK IN BIPOLAR DISORDER: FINDINGS FROM THE LITMUS COMPARATIVE EFFECTIVENESS TRIAL**

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**Objective:** Patients with bipolar disorder suffer from a high rate of comorbid medical conditions, in particular obesity and other cardiometabolic illnesses. This post-hoc analysis examined the role of medical comorbidity and general cardiovascular disorder (CVD) risk on bipolar disorder outcomes and assessed change in overall CVD risk during treatment with lithium as compared with other mood stabilizers.

**Methods:** Data were derived from the Lithium-Treatment Moderate Dose Use Study (LiTMUS), a 6-month, multisite, randomized, parallel-group, single (rater)-blinded trial that evaluated the effectiveness of lithium (n=137; Li) as a component of optimized treatment (OPT) in comparison to OPT alone (n=141). The average risk (percent) of developing any major atherosclerotic CVD event over a 10-year period was calculated using seven cardiovascular risk factors comprising a sex-specific CVD risk score developed from the Framingham Heart Study. The Cumulative Illness Rating Scale and Cornell Services Index were used to rate the burden of comorbid medical illness and medical services use, respectively.

**Results:** In comparison to participants with lower CVD risk, those with greater baseline risk of having a major atherosclerotic CVD event experienced greater improvement in manic symptoms over 24 weeks (p=.05). However, no significant relationships were identified between body mass index (BMI) or medical comorbidity burden and change in depressive or manic symptomatology. Approximately one-third of subjects (n=86) had an estimated 10-year risk of experiencing a major atherosclerotic event between 6% and <20%. After adjustment for age and gender, CVD risk scores increased between baseline and end of study for the Li+OPT (p=.01) but not the OPT group, although no between group differences emerged. Use of medical services occurred more often by participants with higher CVD risk scores and higher BMI (p <.05 for both).

**Conclusions:** Findings from this comparative effectiveness study suggest that elevated CVD risk is associated with greater improvement in manic but not depressive symptomatology. Similar increases in CVD risk among Li+OPT- and OPT-treated patients suggests that monitoring of CVD risk factors should routinely be employed for all bipolar disorder patients and encourages integrated treatment for mood and physical health problems.

**Learning Objectives:**

- To identify whether medical comorbidity burden and cardiovascular disease risk status affects change in psychiatric symptom severity during the treatment of bipolar disorder
- To determine whether differential changes in cardiovascular disease risk occur during treatment with lithium plus optimized treatment in comparison to optimized treatment without lithium

**Source of Funding:** NIMH Contract #N01MH80001

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**USE OF A NOVEL ADJUNCTIVE CLINICAL TRIAL DESIGN TO EXAMINE EFFICACY, SAFETY OF ARMODAFINIL FOR THE TREATMENT OF BIPOLAR I DEPRESSION**

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**Objectives:** Patients in randomized, controlled trials of bipolar depression are generally not representative of a clinical population. This study attempted to examine a large sample of patients more representative of patients seen in clinical practice. This report presents baseline patient characteristics from a Phase 3 study examining adjunctive armodafinil for the treatment of a major depressive episode associated with bipolar I disorder (NCT01072929).

**Methods:** To assess the safety and efficacy of adjunctive armodafinil 150 mg/day in a heterogeneous sample of patients, this 8-week, double-blind, placebo-controlled, multicenter study evaluated adult patients with bipolar I disorder who were currently experiencing a major depressive episode while taking 1-2 maintenance therapies (mood stabilizers and/or second-generation antipsychotics).

**Results:** The study was conducted at 70 centers in 10 countries from January 2010 to March 2012. Of 786 patients screened, 433 were randomized. Baseline disease severity as assessed by mean (SD) IDS-C<sub>30</sub> total scores was characteristic of moderate depression (43.6 [6.93] and 43.2 [7.76] for the placebo and 150 mg groups, respectively). The most common concomitant treatments were valproate, lithium, and lamotrigine. Patients in the placebo and armodafinil 150 mg groups experienced their first depressive episode 13.8 (SD 10.24) and 14.5 (SD 11.73) years prior to screening, respectively. The number of distinct regimens of adjunctive treatments will also be reported. For the armodafinil 150 mg group compared with placebo, at week 8 there was a significantly greater decrease in LS mean (SEM) IDS-C<sub>30</sub> total score (−21.7 [1.11] vs −17.9 [1.10];  $P=0.0097$ ; Cohen's  $d$  therapeutic effect size = 0.28).

**Conclusions:** Because the design allowed a wider range of adjunctive maintenance therapies, subjects enrolled in this study may be more representative of patients in clinical practice. The diversity of therapeutic regimens encountered in this study may improve external validity/generalizability without sacrificing assay sensitivity, although a large sample size was necessary. Further studies are needed to explore how research on bipolar depression treatments can improve external validity by employing more inclusive designs without sacrificing assay sensitivity.

This study was on an investigational use of armodafinil.

**Learning Objectives:**

- To examine a large sample of patients more representative of those seen in clinical practice than those generally included in randomized, controlled trials of bipolar depression
- To study characteristics of the resulting patient population at baseline

**Source of Funding:** Teva Pharmaceuticals

**Literature References:**

- Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA: Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry* 2010; 71(10):1363-1370.
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**A POST HOC ANALYSIS OF EFFICACY AND TOLERABILITY OF LURASIDONE  
ADJUNCTIVE TO EITHER LITHIUM OR VALPROATE FOR THE TREATMENT OF  
BIPOLAR I DEPRESSION**

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**Background:** Bipolar depression is a chronic, disabling illness with few approved treatments, and none are approved for adjunctive use with mood stabilizers. PREVAIL 1 study evaluated the efficacy and safety of lurasidone (LUR) 20-120 mg/d adjunctive to either lithium (Li) or valproate (VPA) in patients with bipolar I depression. This post hoc analysis compared the efficacy and tolerability of adjunctive LUR vs placebo (PBO) by respective mood stabilizer use.

**Methods:** In this randomized, double-blind, PBO-controlled, 6-week study, patients with nonpsychotic bipolar I depression, with or without rapid cycling (DSM-IV-TR), received flexibly dosed LUR 20-120 mg/d (N=179) or PBO (N=161) adjunctive to Li or VPA (therapeutic levels for  $\geq 4$  weeks prior to study entry and maintained during the study). Change from baseline in MADRS total and Clinical Global Impressions Bipolar, Severity of Illness (CGI-BP-S) depression total scores were analyzed by MMRM. MADRS response ( $\geq 50\%$  reduction) and remission (MADRS  $\leq 8$ ) were analyzed by logistic regression. Safety and tolerability were monitored throughout.

**Results:** Mean baseline MADRS scores were similar for the Li and VPA subgroups (range 30.5-31.0). In the overall population, statistically significant improvement from baseline to 6-week end point was observed for LUR vs PBO in MADRS score (-17.1 vs -13.5;  $p=0.005$ , Cohen's  $d=0.34$ ) and in CGI-BP-S score (-1.96 vs -1.51;  $p=0.003$ , Cohen's  $d=0.36$ ). A similar pattern of MADRS score change was observed when LUR vs PBO was added to Li (-18.3 vs -14.2;  $p=0.025$ , Cohen's  $d=0.38$ ) or VPA (-17.2 vs -14.0,  $p=0.07$ , Cohen's  $d=0.29$ ) and for CGI-BP-S score change (-2.0 vs -1.56,  $p=0.055$ , Cohen's  $d=0.33$ , Li subgroup; -1.96 vs -1.51,  $p=0.031$ , Cohen's  $d=0.34$ , VPA subgroup). MADRS response rates were statistically significant for the LUR vs PBO in the overall population (57% vs 42%;  $p=0.008$ , NNT=7) with a similar pattern of change in MADRS when added to Li (61% vs 47%,  $p=0.087$ , NNT=8) or VPA (53% vs 38%,  $p=0.050$ , NNT=7). Significantly higher MADRS remission rates were observed for the LUR vs PBO in the overall population (40% vs 22%,  $p<0.001$ , NNT=6) and when added to Li (47% vs 26%,  $p=0.007$ , NNT=5) or VPA (34% vs 18%,  $p=0.023$ , NNT=7). LUR treatment was generally well tolerated; the most common AEs ( $\geq 5\%$  and more than PBO) were nausea, tremor, and akathisia for LUR adjunctive to Li, and nausea and somnolence for LUR adjunctive to VPA. Akathisia was reported by 10.8% for LUR vs 8% for PBO (Li subgroup, NNH=36) and by 4.4% for LUR vs 1.1% for PBO (VPA subgroup, NNH=31). Discontinuations due to AEs were similar for LUR vs PBO when added to Li (4.3% vs 9.1%) or VPA (7.8% vs 6.8%).

**Discussion:** In this post hoc analysis, LUR adjunctive to either Li or VPA in bipolar I depression was similarly effective and well tolerated.

**Learning Objectives:**

- Lurasidone when administered adjunctively to lithium is effective and well tolerated in the acute treatment of bipolar I depression compared with placebo.



- Lurasidone when administered adjunctively to valproate is effective and well tolerated in the acute treatment of bipolar I depression compared with placebo.

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

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**SUICIDAL RISK IN OUTPATIENTS WITH BIPOLAR DISORDER: FINDINGS FROM THE BIPOLAR CHOICE STUDY**

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**Objective:** Bipolar disorder is a lifelong, chronic, and highly recurrent mood disorder characterized by episodes of mania (or hypomania) that alternate with episodes of major depression.<sup>1</sup> Major depressive episodes in bipolar disorder are associated with 25-56% of lifetime suicide attempts and 10-19% of deaths by suicide.<sup>2</sup> Thus, the monitoring of suicidality in bipolar disorder is essential. However, few brief, reliable, self-report ratings of suicidal ideation and behavior exist that can be used in both research and clinical settings. In research, suicide is often assessed using a diagnostic tool (e.g. MINI), a mood rating (e.g. the Bipolar Inventory of Symptoms Scale; BISS), or an explicit questionnaire about suicidal behavior (e.g. the Columbia Suicide Severity Rating Scale; CSSRS). The Concise Health Risk Tracking Scale (CHRT) is a novel 7 item self-report measure developed to assess suicidality in patients with major depression, but has not been used in bipolar disorder.<sup>3</sup> The purpose of this paper is to compare the suicide tracking assessments used in the CHOICE study.

**Methods:** The Bipolar CHOICE study is a nationwide, multi-site comparative effectiveness trial funded by AHRQ, comparing lithium and quetiapine. Subjects were randomized to receive either lithium or quetiapine along with personalized adjunctive treatment, and monitored by study physicians and blinded raters over six months. We examined the baseline clinical characteristics related to suicide using the CSSRS, BISS, Clinical Global Impression Scale – Bipolar Version (CGI-BP), and MINI suicide scale. We plan to investigate how these measures are related to the CHRT.

**Results:** Our sample consisted of 484 outpatients diagnosed with Bipolar I Disorder (68.2%) or Bipolar II Disorder (31.8%); 58.9% were females and 71.9% were Caucasian. Patients had a mean CGI-BP score of 4.5 (SD = 1.1), and a mean BISS suicide item score of 0.7 (SD = 1.0), consistent with a substantial number of patients having current active suicidal ideation. 38.8% of our sample had attempted suicide in the past, and 18.5% had an interrupted or aborted attempt. On the MINI suicide module, 16.1% were considered at high risk, 13.2% at medium risk, 60.5% at low risk, and only 10.1% at no risk. Relationships between the CHRT total score, CHRT individual items and the other measures of suicide history, ideation, and behavior will be presented.

**Conclusion:** Even though the inclusion criteria for CHOICE only required participants to be at least mildly ill (CGI  $\geq$  3), patients, on average, were moderately-markedly ill, often had a history of suicide attempts, and had baseline measures of suicidality suggesting that they continued to be at risk for suicide.

We predict that the CHRT will be significantly related to these measures of suicidal ideation and behavior.

**Learning Objectives:**

- The validity of a self-report suicidal risk scale in BD
- Examine clinical correlates of suicidal risk in BD

**Source of Funding:** AHRQ: 1R01HS019371-01

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**CLINICAL CORRELATES OF STAGE OF ILLNESS AND PREDOMINANT POLARITY IN BIPOLAR DISORDER.**

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**Objective:** Bipolar disorder (BP) is a chronic disorder, with a high risk for suicide, disability and substance use. The number and pattern of prior mood episodes may be useful in predicting clinical features and treatment response. Staging, based on the number of total mood episodes, and predominant polarity (PP) are two methods that use mood episodes to categorize BP. Having more past mood episodes has been associated with worse functioning, and poorer quality of life<sup>1</sup>. A depression PP (PPD) has been associated with more past suicide attempts and more antidepressant and lamotrigine use, while a manic PP (PPM) has been associated with more frequent antipsychotic use and diagnosis of bipolar I vs. II<sup>2</sup>. We used the number of prior mood episodes to categorize participants into 3 stages ( $\leq 5$  mood episodes, 6-10 and  $>10$ ). PP was defined if  $>2/3$  of past mood episodes were either depressed (PPD) or manic/hypomanic (PPM). We predicted that those with higher number of past episodes and those with PPD will have a worse outcome, more disability and suicide attempts.

**Methods:** A total of 358 individuals (295 BPI and 63 BP II) completed the Diagnostic Interview for Genetic Studies (DIGS) and provided information about clinical features and past mood episodes. Baseline features included history of past suicide attempts, any substance use disorder (excluding nicotine), past history of mixed states, rapid cycling, psychosis, comorbid anxiety disorders and disability due to psychiatric illness. Participants also completed the Childhood Trauma Questionnaire (CTQ) and a subset of the individuals (N=169, 47%) completed a longitudinal interval follow up evaluation (LIFE) in the follow up period (Mean=119 weeks, S.D. 34). We also compared clinical features during the follow up period between the groups.

**Results:** The staging groups were not statistically different on education levels or substance use disorder history, but were different in all other variables with the group with  $>10$  past episodes being older at time of study entry ( $P<0.001$ ), having a younger age of onset ( $P<0.001$ ), more female ( $P=0.013$ ), and having more rapid cycling ( $P<0.001$ ), mixed episodes ( $P<0.001$ ), disability ( $P=0.004$ ), comorbid anxiety ( $P=0.003$ ), BP II diagnosis ( $P=0.006$ ), higher levels of childhood trauma ( $P<0.001$ ) and history of suicide attempts ( $P=0.001$ ), but lower rates of psychosis ( $P=0.002$ ). At two year follow up, the group with  $>10$  episodes had higher rates of disability ( $P=0.003$ ) and more mixed episodes ( $P=0.011$ ), but no significant differences in rapid cycling, substance abuse, psychosis or suicide history. Comparing the same clinical features based on PP, only showed significance for higher rates of rapid cycling at baseline for PPM ( $P=0.005$ ).

**Discussion:** The number of past mood episodes in bipolar disorder is correlated with important clinical features such as suicide, disability, psychosis, mixed features and rapid cycling. A history of childhood trauma is associated with a risk of having more mood episodes. More frequent mood episodes are also prospectively associated with mixed episodes and disability. However, the use of predominant polarity to categorize participants was of limited value in our sample.

**Learning Objectives:**

- Higher number of prior mood episodes is associated with clinical features indicating poor outcome.
- Childhood trauma is associated with risk of more frequent mood episodes.

**Source of Funding:** H.C. Prechter Research Fund.

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**ABNORMAL NEURAL ACTIVITY DURING HIGH MEMORY LOAD WORKING MEMORY PERFORMANCE DISTINGUISHES BIPOLAR DISORDER FROM UNIPOLAR MAJOR DEPRESSION IN DEPRESSED ADOLESCENTS**

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Depressive episodes are the first and most common manifestation of BP in youth (1, 2), however; it is difficult to clinically differentiate the symptoms of BP depression from those of MDD (3). Furthermore, failure to differentiate BP depression (BPd) from the depression of major depressive disorder (i.e., MDD or unipolar depression) in youth has significant clinical consequences and may result in contraindicated interventions such as antidepressant monotherapy.

In this functional MRI study we aimed to identify neural activity during Emotional N-back performance in depressed youth that may differentiate BP (BPd) from Major Depressive Disorder (MDD).

Using fMRI Tesla 3, an Emotional N-Back Working memory Task (EFNBACK) was employed to study emotion processing in 12 BPd (7 with BP I and 5 with BP II; 9 females and 3 males, age= 15.5±1.2) compared to age- and gender-matched 10 MDD and 10 Healthy Control (with no family history of BP) Adolescents.

Neural activity was significantly different between the groups during the 2n-back high memory load of the task with and without fearful face distractors. During the fearful face distractors condition of 2n-back task, adolescents with BPd had lower activity in lower right and left posterior cingulate (BA 30) compared to MDD group and in right posterior cingulate (Brodmann's Area, BA, 31), right anterior cingulate (BA 24), left supplementary motor (BA 6) regions compared to both MDD and HC groups whereas adolescents with MDD had higher activity in right and left posterior cingulate (BA 30) compared to HC. In contrast, when there were no emotional face distractors of the 2n-back high memory load of the task, adolescents with BPd had higher activity in anterior cingulate (BA 24) compared to MDD and HC groups whereas adolescent with MDD had lower neural activity in this region compared to HC.

BPd youth relative to MDD and HC youth showed decreased posterior and anterior cingulate and middle frontal neural activities when distracted by emotional stimuli but increased anterior cingulate activity when there was no emotional distraction suggesting that when emotional distractors were present adolescents with BPd had difficulty in recruitment of their neural regions associated with processing of working memory. Adolescents with BPd had more recruitment of their affective region of cingulate when there were no emotional distractors suggesting an abnormally hyperactive affective circuitry.

Our results showed that neural activity during processing of working memory can help differentiate BP from MDD in depressed youth and the presence of emotional distractors altered the direction of the difference between groups. We need larger longitudinal studies to better understand clinical correlates of mood-specific versus disease-specific neural activity in BPd versus MDD youth that may inform imaging-guided differential diagnosis and treatment approaches.

**Learning Objectives:**

- Significance of identification of depression in the course of bipolar disorder in adolescents
- Neural activity during working memory performance can help differentiate bipolar from unipolar depression in adolescents

**Source of Funding:** This study is supported by the American Academy of Child and Adolescent Psychiatry Ryan Licht Sang Foundation Quest for the Test Award.

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**EFFICACY OF CARIPRAZINE ON YMRS SINGLE ITEMS: A POOLED ANALYSIS OF 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS IN BIPOLAR MANIA**

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**Background:** Cariprazine (CAR) is an orally active and potent dopamine D<sub>3</sub>/D<sub>2</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors currently in development for the treatment of mania. Bipolar mania is a debilitating disease for which optimal clinical treatments require broad antimanic efficacy. CAR has demonstrated efficacy in 3 randomized, double-blind, placebo-controlled trials (NCT01058096, NCT01058096, NCT01058096) in bipolar mania. This pooled analysis evaluated the effects of CAR on YMRS single-items to investigate efficacy across mania symptom domains.

**Methods:** Data were pooled from 3 cariprazine studies in patients with acute manic or mixed episodes associated with bipolar I disorder. CAR was flexibly dosed (3-12 mg/day) in 2 studies; the third study used a fixed/flexible dose design (3-6 mg/day, 6-12 mg/day). All 3 studies consisted of a washout period of up to 7 days followed by 3 weeks of double-blind treatment. Patients were hospitalized for screening and ≥14 days of treatment. Post hoc pooled analysis analyzed change from baseline to Week 3 in individual items of the Young Mania Rating Scale (YMRS) using an MMRM approach.

**Results:** A total of 1037 patients (CAR, n=608; PBO, n=429) were included in the pooled ITT population, defined as patients who received ≥1 dose of study medication and had ≥1 postbaseline YMRS assessment. In each of the individual trials, CAR showed significant advantage vs PBO on YMRS total score improvement (LSMD: -4.3 to -7.0;  $P < .0001$  [all studies]). In the pooled analyses, the LSMD for CAR vs PBO was significant for all YMRS items: elevated mood (-0.38 [95% CI: -0.53, -0.24],  $P < .0001$ ), increased motor activity-energy (-0.34 [95% CI: -0.49, -0.18],  $P < .0001$ ), sexual interest (-0.29 [95% CI: -0.42, -0.17],  $P < .0001$ ), sleep (-0.33 [95% CI: -0.48, -0.19],  $P < .0001$ ), irritability (-0.85 [95% CI: -1.07, -0.63],  $P < .0001$ ), speech (-0.69 [95% CI: -0.93, -0.46],  $P < .0001$ ), language (-0.33 [95% CI: -0.46, -0.20],  $P < .0001$ ), content (-0.78 [95% CI: -1.05, -0.51],  $P < .0001$ ), disruptive-aggressive behavior (-0.69 [95% CI: -0.89, -0.50],  $P < .0001$ ), appearance (-0.23 [95% CI: -0.33, -0.13],  $P < .0001$ ), and insight (-0.24 [95% CI: -0.34, -0.14],  $P < .0001$ ). In general, CAR treatment showed at least moderate effect sizes (Cohen's *d*) on all YMRS items, with estimates ranging from -0.31 (increased motor activity) to -0.55 (irritability).

**Conclusion:** Cariprazine demonstrated efficacy on all individual YMRS items in this pooled analysis. These results suggest that cariprazine has broad efficacy across symptoms in the treatment of acute mania associated with bipolar I disorder.

**Learning Objectives:**

- Understand the broad efficacy profile of cariprazine in the treatment of acute mania associated with bipolar I disorder
- Identify key symptom domains and understand treatment effect of cariprazine in these domains

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

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**A DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL OF ADJUNCTIVE ARMODAFINIL FOR THE TREATMENT OF MAJOR DEPRESSION ASSOCIATED WITH BIPOLAR I DISORDER**

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**Objectives:** The goal of this study was to evaluate the efficacy and safety of armodafinil as an adjunctive therapy for major depression associated with bipolar I disorder.

**Methods:** Patients 18-65 years of age with bipolar I disorder currently experiencing a major depressive episode while taking 1 or 2 mood stabilizer(s) and/or second-generation antipsychotic(s) were randomized. The primary outcome was the mean change from baseline to week 8 in the 30-item Inventory of Depressive Symptomatology–Clinician-rated (IDS-C<sub>30</sub>) total score.

**Results:** 433 patients were randomized (n=199 placebo, n=201 armodafinil 150 mg, n=33 armodafinil 200 mg). Randomization to the 200 mg armodafinil group was discontinued early; only safety results from this group are presented. For the armodafinil 150 mg group compared with placebo, there was a significantly greater decrease in LS mean (SEM) IDS-C<sub>30</sub> total score (–21.7 [1.11] vs –17.9 [1.10];  $P=0.0097$ ; Cohen's  $d$  therapeutic effect size = 0.28) at week 8 and the percentage of IDS-C<sub>30</sub> responders ( $\geq 50\%$  decrease from baseline) was significantly greater at week 8 (55% vs 39%;  $P=0.0084$ ) and final visit (46% vs 34%;  $P=0.0147$ ). The most common AEs were headache (9.6% vs 10.1%), diarrhea (8.6% vs 6.5%), and nausea (5.6% vs 4.5%) for the armodafinil 150 mg and placebo groups, respectively, and headache (21.9%), insomnia (12.5%), and nausea (9.4%) for the armodafinil 200 mg group. At final visit, 5% (9/183) of patients in the placebo group, 2% (3/186) of the 150 mg group, and 4% (1/28) of the 200 mg group had potentially clinically significant ( $\geq 7\%$ ) weight gain from baseline.

**Discussion:** Armodafinil 150 mg significantly improved depressive symptoms compared with placebo in patients with a major depressive episode associated with bipolar I disorder when given as adjunctive treatment to mood stabilizers. Safety data indicate that adjunctive armodafinil 150 mg was generally well tolerated.

This study was on an investigational use of armodafinil.

**Learning Objectives:**

- To examine the efficacy of armodafinil as an adjunctive therapy for major depression associated with bipolar I disorder
- To determine the safety of armodafinil administered as an adjunctive therapy with 1 or 2 mood stabilizer(s) and/or second-generation antipsychotic(s)

**Source of Funding:** This study was funded by Teva Pharmaceuticals.

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## COMPARISON OF SUICIDALITY BETWEEN SMOKERS AND NON-SMOKERS IN AN ADULT IN-PATIENT PSYCHIATRIC SETTING USING THE SHEEHAN- SUICIDALITY TRACKING SCALE

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**Purpose:** Suicide and smoking are two major public health concerns. Furthermore, epidemiological-based studies indicate a relationship between suicidal behavior and smoking (1). Few studies have examined the relationship between smoking and suicidality with psychiatric samples. Clinical suicidologists have called for a unified operational definition for suicidal behaviors, which will contribute to a systematic collection of reliable data (2). The purpose of this secondary analysis is to compare adult, psychiatric in-patient smokers and non-smokers using a systematic and structured suicide assessment, the Sheehan-Suicidity Tracking Scale (S-STTS) (3).

**Method:** Secondary analysis of 200 adult psychiatric in-patients who participated in the original psychometric evaluation study comparing three different suicide assessments. The mean age of participants was 38.6 (*SD*=12.4). The original study did not screen for tobacco use or smoking behaviors. The S-STTS was administered as an interview or self-report following randomization and counter-balancing sequence protocols. The S-STTS created three composite scores including suicidal ideation, suicidal behavior, and a total suicidality score. Smoking or cigarette use was identified with a dichotomous item included on a comprehensive risk assessment interview.

**Results:** Descriptive data revealed an approximately even split between smokers (51%, *N* = 103) and non-smokers (49%, *N* = 97). Gender characteristics for the smokers included 52 men and 51 women. For the non-smokers, the gender breakdown was 35 men and 62 women. The average past month S-STTS composite score for smokers was 14.4 (*SD*: 10.0) and 15.5 (*SD*: 10.4) for non-smokers in the psychiatric sample. The average suicidal ideation score was 11.5 (*SD*: 7.8) for smokers and 12.6 (8.4) for non-smokers. Lastly, smokers had an average suicidal behavior scores of 2.3 (2.6) compared to 2.2 (2.6) for non-smokers. Student's *t*-test was conducted to examine whether any significant differences exist between smokers and non-smokers on suicidality outcome scores. There were no significant differences between smokers and non-smokers on suicidal ideation,  $t = .91(197 \text{ df})$ ,  $p > .05$ , suicidal behavior,  $t = -.15(197 \text{ df})$ ,  $p > .05$  or the total suicidality composite score,  $t = .79$ ,  $p > .05$ . Effect sizes were small, Cohen's  $d = .02$  to  $.13$ , where  $.20$  is generally considered "small."

**Significance:** The results of this analysis are significant for the literature as it represents the first empirical evidence comparing smokers and non-smokers using a standardized and structured suicide assessment evaluating both behavior and ideation in an inpatient psychiatric setting. Results indicate no significant differences in suicidality between smokers and non-smokers. These findings relate to major epidemiological studies where researchers found insignificant associations once controlling for mental health variables (4). The relationship between suicide and smoking may have strong empirical findings with community samples, but further research is needed with psychiatric samples.

## Learning Objectives:

- Examine the relationship between suicidality and smoking in an in-patient psychiatric setting.

- Difference in the outcome of the historical relationship between suicidality and smoking when using a systematic suicide assessment scale.

**Source of Funding:** This study was supported by an investigator initiated award from Pfizer, Inc. to Penn State Hershey Medical Center (Alan Gelenberg, MD PI).

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#### **WHEN ARE YOUR TRIAL DATA REAL**

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In the current highly controlled and rigorous FDA drug approval process, conducting a randomized clinical trial (RCT), with a multiple baseline or crossover design can be extremely expensive. Thus, most researchers who are examining new compounds or those who might be examining existing compound in order to expand the acceptable area of therapeutic effectiveness face some rather challenging hurdles, particularly with respect to the effects a compounds impact on cognition and/or emotions. Failed clinical trials can cost companies tens of millions of dollars. Thus, there is good reason to examine any reasonable cause of a RCT to determine the most likely cause of the failed trial. As a rule of thumb, most drug trials going from Phase I through to Phase III have approximately only a 25% success rate. For drugs that involve the therapeutic goal of enhancing cognition and or affect, or for those whose purpose is to have a therapeutic impact of affect, while leaving cognition intact, substantiating the cognitive performance of participants in the trial (i.e. therapeutic patients or normal controls) is essential. Recent research, primarily focused in the area of clinical neuropsychology and specifically forensic neuropsychologists, found certain assessment methods and statistical procedures are effective in reliably identifying suboptimal effort (i.e., invalid test scores). Such methods are more typically used when participants clearly have issue often referred to as secondary gain (e.g., workers compensation, civil litigation, veterans' benefits, and/or Social Security Disability Insurance). Our research team has found that suboptimal cognitive test performance is far more common than most would think and this is evident for both experimental subjects as well as normal controls. We will present evidence of suboptimal effort in baseline, drug, and placebo trials and make recommendations as to how to controls of these factors and design trials to take such factors into account. Granted, the reasons for participants to produce invalid test scores may be different between civil litigation claimants and participants in a therapeutic trial, and the base rates for invalid effort are likely lower than what might be expected in a sample of subjects who have obvious secondary gain at stake. However, the data from this drug trial, which uses a baseline, and crossover design (clinical and placebo randomized design) will clearly show how several subjects performed at less than optimal levels for no obvious reason but the results would lead one to conclude falsely that the drug has a negative impact on cognition, which we are able to show is not true. The dataset, which involves the administration of Lorazepam, which has known cognitive impairing effects, will be used to substantiate that poor effort by approximately 30% of the examined sample who failed to complete tasks by putting forth optimal effort would result in most drug trial researchers in concluding that the results were that of a failed trial,

with the concomitant loss of resources that were spent on the trial. However, with adequate statistical analyses, such a conclusion is not only found to be incorrect but reversible, saving valuable data and resources in the long run.

#### **Learning Objectives:**

- Recognize non-volitional disruptions of neuropsychological testing when they occur, based on performance patterns across neurocognitive and SVT measures as well as consideration of clinical history.
- Recognize that useful clinical data can be obtained even in assessments that might be invalid or impacted by suboptimal effort by participants.
- Develop strategies for dealing with assessment results impacted by non-volitional factors and learn to incorporate these findings into a cohesive, informative report.

#### **Literature References:**

- Green, P., Rohling, M. L., Lees-Haley, P., & Allen, L. M. (2001). Effort accounts for more neuropsychological test variance than does ability in litigant sample. *Brain Injury*, 15, 1045-1060.
- Rohling, M. L. & Boyd, A. (June, 2011). The Automation of Cognitive Assessment in Clinical Trials: Strategies and Methods to Produce a Stable Neurocognitive Baseline at Randomization: Perspectives from CNS Vital Signs. Paper presented at the 51st annual conference of the American Society for Clinical Psychopharmacology in Boca Raton, FL.

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#### **A PRESENTATION OF THE CURRENT WORKING VERSION OF THE ROSENBERG-HASSMAN MOOD SCALE (RHMS): A FREQUENCY-BASED DEPRESSION INVENTORY**

Leon Rosenberg, M.D.; Board Certified Psychiatrist<sup>1</sup>, Howard Hassman, D.O.<sup>2</sup>, Keith Wesnes, PhD<sup>3</sup>, David G. Krefetz, DO, MBA<sup>2</sup>

<sup>1</sup>Center for Emotional Fitness, <sup>2</sup>CRI Lifetree, <sup>3</sup>Bracket

**Background:** Patient-Reported Outcome (PRO) scale development is a repetitive process. Over the last 2 years we have complied with the following Step I and II suggestions from the 5-Step FDA Guidance for PRO development<sup>1</sup>:

- Outline hypothesized concepts and potential claims
- Determine intended population
- Perform literature/expert review
- Document preliminary instrument development
- Obtain patient input
- Generate new items
- Select recall period (RP), response options (RO), and response format (RF)
- Select method of administration/data collection

The Rosenberg-Hassman Mood Scale (RHMS) is based on the concept that symptom frequency is the best measure of disease severity and change. RHMS measures Major Depressive Episode (MDE) symptom frequency over the last 7 days.

A literature review<sup>2</sup> provided the following useful guidelines:

1. The magic number (of RO for each item) is 7 plus or minus 2
2. The use of only 5 RO reduces reliability by 12%
3. Give the rater an unequivocal conception of the continuum to evaluate
4. RO should not be discontinuous
5. There should be a constant interval between RO, excluding endpoints
6. All RO should have nearly identical word counts
7. With fewer than 20 items weighting of items may be needed

An expert review suggested:

1. Distress and impairment must be measured, but in a way that avoids systematic errors related to unemployment, re-employment and vacations
2. Use a 7 day not a 3 day RP



3. Confirming every answer may not be user friendly
  4. Have more than the 5 RO in the Hamilton Depression Scale and more than the *de facto* 4 RO in the Montgomery Asberg Depression Rating Scale
- For response options we selected these 7 frequency RO:

0	0%
1	1 to 19%
2	20 to 39%
3	40 to 59%
4	60 to 79%
5	80 to 99%
6	100%

### Method

Over the last year input has been obtained from:

1. 25 clinicians regarding 9 different RF
2. 20 patients regarding the same 9 RF
3. 68 patients regarding 326 word/phrase sub-symptoms in 23 non-suicide categories

### Results

1. 25 clinicians clearly preferred 4 of the 9 RF
2. 20 patients clearly preferred 4 of the 9 RF
3. 3 of the 4 RF the patients preferred were the same that clinicians preferred
4. 228 of the 326 word/phrases were endorsed by 65% of patients as appropriately categorized

### Discussion

- For each of the non-suicide categories, only sub-symptoms with 65% or more agreement have been included in the RHMS.
- Research has resulted in the RHMS having 24 questions, 21 consistent with the DSM-IV MDE criteria plus 1 each for irritability, physical anxiety, and emotional anxiety.
- These 3 additional categories were endorsed at greater than 65%.
- RHMS computerized version 1.0 has been created and is undergoing Step II pilot testing and Step II patient cognitive interviewing.
- RHMS 1.0 takes 10 to 15 minutes to complete.

### Learning Objectives:

- FDA Guidance for PRO development suggests documentation and specific steps to take to validate a PRO including literature/expert review and repeated patient input.
- The magic number (of RO for each item) is 7 plus or minus 2

**Source of Funding:** None

### Literature References:

- Streiner DL and Norman GR: Health Measurement Scales, NY, Oxford University Press, 2008
- FDA: Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, U.S. Department of Health and Human Services, December 2009

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## THE APPLICATION OF COGNITIVE NEUROSCIENCE TO CLINICAL RESEARCH I: DETECTING COGNITION ENHANCEMENT IN MAN

Keith Wesnes, PhD<sup>1</sup>

<sup>1</sup>Bracket

**Introduction:** As human longevity steadily grows in more fortunate world regions; cognition enhancement has become a 'hot topic' and is currently arousing intense public and scientific debate. While definitions vary, cognition enhancement can be defined as improved ability to perform tasks involving mental ability; either by counteracting impairment, or by producing improvement above

existing levels. The principal and arguably only direct and objective measure of cognitive ability involves the use of tasks that demand mental efficiency. This paper concerns a computerised test system designed by the author which had its roots in a PhD project at Reading University (UK) which began in 1972 to determine whether the brain reticular cholinergic systems were involved in the control of human attention. It rapidly became evident that to detect subtle cognitive improvements in healthy students, automated procedures that captured cognitive reaction times as well as accuracy were essential. The early laboratory computers of the 1970s offered the first solutions, while portable laboratory microcomputers allowed cognitive testing to migrate from the laboratory to diverse clinical settings and even patients home in the early 1980s.

**Methods:** The system which emerged from this early research and upon which this presentation is based has been used in over 1300 trials worldwide. The core tests cover attention, information processing, working memory, executive control, and various aspects of verbal and non-verbal episodic memory. The core tests have remained constant over the last 29 years and have been supplemented with others. The public domain studies in which the system has identified cognition enhancement are reviewed in this paper. Three major domains are evaluated (1) Attention/information processing, (2) Working memory/executive control, and (3) Episodic memory. For each study the Tables indicate whether or not the domain was assessed, and if so whether significant improvement was identified, or significant impairment, or no reliable change.

**Results:** 175 studies were identified published in 125 peer-reviewed journals, 7 chapters & 1 review; as well as 39 other studies published as abstracts from conference presentations and 3 unpublished conference presentations. The 5 peer-reviewed negative studies are additionally included for completeness, including one published by JAMA who considered it a well conducted negative trial. The trials which were conducted from 1975 to the present involve data from over 11,000 healthy volunteers aged 5 to 87 years & 26 different patient populations. The interventions include pharmaceuticals, nutraceuticals, natural products, everyday drugs including those of abuse, various surgical procedures and even classroom ventilation.

**Conclusions:** To the author's knowledge, this is the largest database ever assembled of cognitive enhancement identified with a single test or test system. The answer to the question of whether a single system can be used in a diverse range of conditions to detect cognition enhancement appears to be a positive one. Further work will include the identification of the relative effect sizes of the various improvements in all of the studies.

**Learning Objectives:**

- Learn whether a single test system could be used in a wide variety of clinical indications and different study designs to successfully and consistently identify cognition enhancement
- Learn about the crucial features of cognitive tests which enable them to reliably detect cognition enhancement in man

**Source of Funding:** The majority of the 175 studies reviewed have been sponsored by the pharmaceutical and nutraceutical industries

**Literature References:**

- Wesnes KA (1977). The effects of psychotropic drugs on human behaviour. *Modern Problems of Pharmacopsychiatry* 12: 37 58.
- Wesnes KA, Warburton DM (1984). Effects of scopolamine and nicotine on human rapid information processing performance. *Psychopharmacology* 82: 147 150.

**DIFFERENTIAL EFFECTS ON ATTENTION OVER 24 WEEKS OF A NMDA ANTAGONIST VERSUS CARBAMAZEPINE IN PEDIATRIC PATIENTS WITH FIRST TIME DIAGNOSED EPILEPSY**

Keith Wesnes, PhD<sup>1</sup>, Joan Busner, Ph.D.<sup>2</sup>

<sup>1</sup>Bracket, <sup>2</sup>Penn State College of Medicine, and Bracket

**Background:** Remacemide hydrochloride, a low-affinity NMDA receptor antagonist with sodium channel-blocking activity, was compared to carbamazepine in a Phase III, double-blind, parallel group, sequential design in newly diagnosed, previously unmedicated, epilepsy patients aged 12 to 75 years (Brodie et al, 2002). The trial planned to have 1000 completed patients and was conducted in 21 countries in Europe, Latin America and Australasia. The study was terminated after 570 patients had been enrolled as interim analysis identified carbamazepine to be significantly superior to remacemide in preventing seizure recurrence. Analysis of cognitive function using automated tests (the CDR System) found attention to be selectively and significantly impaired by carbamazepine whereas improvements were seen with remacemide (Wesnes et al, 2009). This was consistent with previous healthy volunteer work with the same tests which identified remacemide to be free from cognitive impairment, while carbamazepine selectively impaired attentional processes. This is the first analysis of the cognitive effects in the sub-population aged 12 to 17 years.

**Methods:** 92 patients were aged 12 to 17 at study entry and their performance was analysed using repeated measures mixed-model ANOVA.

**Results:** Power of Attention, a validated factor score which combines the speed scores from the 3 CDR System tests of attention (simple reaction time, choice reaction time and digit vigilance) showed a highly significant main effect of treatment ( $p=0.0001$ ; remacemide v carbamazepine) which did not interact with the repeated visits. At 8 weeks, the decrease in reaction time with remacemide (-69 ms, 95% CI -15,-123) was significantly different ( $p=0.0059$ ) from the lengthening with carbamazepine (38 msec, 95% CI -13, 88); the effect size of the difference using Cohen's method was  $d=0.72$ . At 24 weeks, the decrease with remacemide (-81 ms, 95% CI -20,-142) was again significantly different ( $p=0.0055$ ) from the lengthening with carbamazepine (46 msec, 95% CI -17, 109); the effect size was  $d=0.86$ . At baseline, compared to age-matched normal controls, the patients had a deficit of 121 ms. Thus by 24 weeks remacemide had reduced this impairment by 67%, whereas carbamazepine had increased it by 38%.

**Discussion & Conclusions:** In this study a low-affinity NMDA receptor antagonist served to reduce substantially a disease related impairment to focussed attention and information processing in children aged 12 to 17, whereas a widely used and more effective seizure control agent increased the deficit; at 24 weeks the difference constituted a large clinical effect size. This suggests that in this young and maturing population, novel NMDA antagonists more effective in seizure control than remacemide may provide a superior outcome to this core aspect of cognitive function than compounds such as carbamazepine.

Brodie M et al (2002). Efficacy and Safety of Remacemide versus Carbamazepine in Newly Diagnosed Epilepsy: Comparison by Sequential Analysis *Epilepsy & Behavior* 3: 140–146.

Wesnes KA, Edgar C, Wroe SJ, Dean ADP (2009). The cognitive and psychomotor effects of remacemide and carbamazepine in newly diagnosed epilepsy *Epilepsy & Behavior* 14: 522-528.

#### **Learning Objectives:**

- The attendee will become familiar with methods for assessing the objective cognitive consequences of sedating medications in pediatric epilepsy trials.
- The attendee will appreciate the potential benefits of newer compounds with less cognitive side effects than traditional medications in pediatric patients

**Source of Funding:** AstraZeneca

#### **Literature References:**

- Brodie M et al (2002). Efficacy and Safety of Remacemide versus Carbamazepine in Newly Diagnosed Epilepsy: Comparison by Sequential Analysis *Epilepsy & Behavior* 3: 140–146.
- Wesnes KA, Edgar C, Wroe SJ, Dean ADP (2009). The cognitive and psychomotor effects of remacemide and carbamazepine in newly diagnosed epilepsy *Epilepsy & Behavior* 14: 522-528.

**Introduction:** Late 2012 saw the start of a new frontier for clinical trials when the FDA approved a yearlong study in which all assessments are made remotely apart from 2 clinician visits. Such trials in which cognitive function was the endpoint would benefit from assessment of mental function which could be conducted remotely from the home or workplace. In the late 1990s the author was involved in the development of a telephone based methodology using interactive voice response for assessing cognitive function, which was successfully used in a number of scientific studies and therapeutic clinical trials. At the start of this millennium an internet methodology was developed which has since been used in a variety of large scale trials. A trial was conducted in 2004 in which 1,386 children aged between 6 to 16 years logged on at school, reported whether or not they had taken breakfast that morning, and then performed a series of cognitive tests of attention and episodic memory. The findings confirmed a previously conducted laboratory trial; children who had breakfast showing superior cognitive function during the morning than those who did not. The present study compares data from a large recently completed internet study of cognitive function, to data from the same tests administered under laboratory conditions.

**Methods:** A website offered feedback on cognitive function. Individuals clicked on the link entered their age and gender, and could perform 4 tests lasting 10 minutes (a 3-minute vigilance task, simple & choice reaction time and picture recognition). Five language versions could be selected: English, Greek, Hungarian, Portuguese & Spanish.

**Results:** Over an 18 month period 120,171 individuals logged on and entered demographics, 111,203 completed the first task and 97,171 all tasks; this latter cohort then receiving graphical feedback on the degree to which they may have favourably exceeded their age-norms. The age range of participants was 4 to 105 yrs, the male:female ratio was 41:59, and 84% were aged 18 to 60. Within this latter cohort the numbers were fairly evenly distributed over 5 year age-bands. Compared to laboratory data the patterns over the age-range on all task measures were directly comparable: young children showing the poorest performance, which subsequently peaked during the late teenage years and declined steadily thereafter. Gender differences were also consistent with laboratory data.

**Conclusions:** This study demonstrates that remote cognitive testing is feasible in a wide range of existing clinical trial applications; while also offering the opportunity to conduct novel types of clinical trials. A few examples of existing trials which would benefit from such a methodology include post-marketing safety (or efficacy) evaluations of novel medicines, remote studies of nutritional products, long-term follow-up studies in childhood cancer survivor cohorts, and the long duration trials which are now starting in the new indication of preclinical Alzheimer's disease. A novel trial opportunity could be the application of such methodologies to web based patient interest groups; where previously untried therapies, perhaps developed or discovered by members, could be evaluated by the groups for potential efficacy.

**Learning Objectives:**

- Learn whether cognitive testing can be reliably conducted over the internet
- Appreciate the novel research areas which such an opportunity presents

**Source of Funding:** Bracket, Wayne, PA, USA

**Literature References:**

- McCue P, Scholey AB, Herman C, Wesnes KA (2002). Validation of a telephone cognitive assessment test battery for use in chronic fatigue syndrome. *Journal of Telemedicine and Telecare* 8 (6): 337-343.
- Wesnes K et al. (2012). Breakfast is associated with enhanced cognitive function in schoolchildren: An internet based study. *Appetite* 59: 646-9

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

**Background:** In response to concerns over high placebo response and high failure rate of antidepressant clinical trials there is a focus towards use of structured interview guides with outside review of rater adherence<sup>1</sup>.

Based on the assumption that these procedures would improve rater performance we hypothesized that raters at Northwest Clinical Research Center (NWCRC) highly compliant with these methods would have better outcome compared to partially compliant raters.

**Method:** We first obtained randomization codes for six clinical trials conducted at NWCRC from 2008-2011. Each trial used the Montgomery-Asberg Depression Rating Scale.

There were six NWCRC raters, each with at least 20 ratings included in our study. Two raters received excellent feedback from outside reviewers and were fully compliant (N patients = 143) to structured interview methods.

Four raters were partially compliant (N patients = 136). Of these, two failed to qualify after outside review, one did not participate in a reviewed trial and one received poor feedback multiple times. Our analysis evaluated antidepressant-placebo differences and response rates of patients assigned to the rater groups.

**Results:** For raters fully compliant to structured interview procedures there was no significant difference in symptom reduction between patients assigned to antidepressants (31%) versus placebo (32%).

The outcome for partially compliant raters was much better. There was a significant difference in symptom reduction for patients rated by partially adherent raters assigned to antidepressants (38%) versus placebo (22%),  $t(df=134)=2.81, p=0.006, d=0.48$ . A significantly greater proportion of patients rated by these raters attained response when assigned to antidepressants versus those assigned to placebo,  $X^2(df=1)=5.29, p=0.02$ .

**Discussion:** Our aim was to evaluate use of structured interviews and outside review guidelines on antidepressant clinical trial outcome.

Contrary to expectations, use of structured interview methods and outside rater review guidelines did little to influence outcome. In fact, raters with styles that fully complied with these methods had worse outcome.

Interestingly, partially compliant raters performed similarly across trials (regardless of design), with similar outcome ( $d=0.48$ ) to analysis of patients enrolled at NWCRC from 1998-2002 ( $d=0.59$ )<sup>2</sup>.

These data have implications for the design and conduct of future antidepressant clinical trials.

#### **Learning Objectives:**

- To evaluate if structured interview guides and outside review of depression ratings during antidepressant clinical trials have increased assay sensitivity.
- To identify factors that influence rater behavior.

**Source of Funding:** No direct funding was received for this study. There are no current external funding sources for this study. All of the authors were salaried by their institutions during the period of writing (though no specific salary was set aside or given for the writing of this paper).

#### **Literature References:**

- Williams and Kobac. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale. The British Journal of Psychiatry 2008;192:52-58.
- Khan et al. Relative sensitivity of the Montgomery-Asberg Depression Rating Scale, the Hamilton Depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials. International Clinical Psychopharmacology 2002;17:281-285.

**Background:** Post traumatic stress disorder has a 6.8% prevalence in non-clinical samples and up to a 34% prevalence among military personnel and sexual assault survivors. It remains a complex and refractory problem and public health need; despite this, few drugs exist to treat the condition.

**Hypothesis:** We proposed that a broadly disseminated, brief, academic-peer reviewed survey of community and contract research investigators (required for implementing a global drug trial for PTSD) could identify obstacles as well as build a research network.

**Methods:** Covance Investigator Relations and Covance Neurosciences jointly disseminated (via email and local phone call from Global Services representatives of Covance to many local entities in Eastern Europe including the Balkans, Latin America, US, Canada, Britain and other EU, Asia) a 5-item survey on feasibility of global PTSD trials. This was followed by planning modules for meaningful focus group engagement (informed by Covance Neuroscience PTSD expertise). A total of 80 investigators were contacted along with scientific advisors to ongoing Department of Defense PTSD drug development initiatives.

**Results:** A feasibility report and assessment was prepared forming the basis of a conference planned for April 2013. The working paper of this conference will be disseminated via the Covance Neuroscience website. Preliminary survey results indicate that barriers include: selected co-morbidities, sample heterogeneity, stigma, and medicolegal dimensions of PTSD including secondary gain. Other more site-specific input (in the form of 1 page narratives from investigators involved in ongoing PTSD studies and other drug studies in populations with PTSD) will be disseminated during the planned conference. Comparison grids with anti psychotic drug development were prepared along with projections of country-specific recruitment rates that integrated the specific site feedback as well as Xcellerate technology results.

**Learning Objectives:**

- For pharmaceutical drug developers and other researchers to better understand obstacles and solutions in PTSD novel drug development, from an investigator network and CRO perspective
- For clinical researchers to learn how to perform feasibility assessments in order to minimize drop-out and implement the most up to date trial methodologies

**Source of Funding:** N/A

**Literature References:**

- Advancing Research Standards for PTSD Interventions: Suggested approaches for designing and evaluating clinical trials: a Meeting Summary (Oct 2008; publication of NIMH, Veterans Affairs Administration and Department of Defense)
- Implementation of an Evidence Based Post-Traumatic Stress Disorder (PTSD) Treatment in Public Sector Settings: NCT01488539

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**A COMPARISON OF IMPUTATION AND ANALYSIS METHODS FOR EXAMINING INFORMATIVELY MISSING DATA: LESSONS FROM CHRONIC PAIN DATA**

Karen Kesler, Herbert Harris

**Objectives:** To evaluate therapies for CNS disorders, we rely on longitudinal data in order to assess both short and long term effects. Unfortunately, this type of study design is susceptible to bias and incorrect conclusions due to missing data. The most problematic source of missing data is subjects dropping out of the study often because of lack of efficacy or side effects. There are a host of imputation and analysis methods commonly employed to combat this problem, but much controversy exists as to which methods give the most valid results. Quantifying the effects of these various potential solutions is intrinsically difficult due to the problem itself—without the knowing what the true results are for the missing subjects, we cannot directly measure the bias or make meaningful comparisons between imputation and analysis methods.

**Methods:** Our approach to this problem involves use of real data from a chronic pain clinical trial to examine the bias induced in longitudinal data by various imputation and analysis methods. We compare these results to determine the best practical strategy for managing this common problem. The trial

examines a control and experimental groups with chronic pain over 4 weeks using a Numeric Pain Rating scale every day. To accurately measure bias, one needs complete data on all subjects as well as the dropout pattern. We have taken the actual data with informative dropouts and carefully created realistic, full data trajectories for all subjects. Together with the known dropout time, we are then able to conduct analyses with a variety of imputation and analysis methods and calculate the actual bias for each one.

We chose several methods to compare:

- “Observation Carried Forward” Imputation: Imputing both the “Last Observation Carried Forward” (LOCF) and the mixture of “Worst Observation (for experimental subjects) and Last Observation (for control subjects) Carried Forward”.
- Population Mean Imputation.
- Random Effects Analysis: No imputation, just using a Mixed Effects Longitudinal model with a random subject effect, with and without controlling for the reason for dropout.
- Pattern Mixture Model

Since our estimate of interest was the difference in pain scores between the two treatment groups, we compared the bias and standard error of that difference, along with the conclusions drawn for testing a hypothesis of no difference between the groups.

#### Results

We found that the imputation methods examined provided less bias than only using completers, but underestimated the variability of the estimate. Random effects models reduced this bias and controlling for the reason for dropout inflated the variance estimate. Pattern mixture models were associated with the lowest bias and largest estimate of variance.

**Conclusions:** We conclude that Pattern Mixture models provide an excellent sensitivity analysis, but for practical purposes are not ideal for a primary analysis. We recommend the random effects models on the longitudinal data. We discuss the generalization of these findings to clinical trial data from other CNS indications.

#### Learning Objectives:

- To develop an appreciation of the various methods commonly used to handle the problem of missing data in clinical trials in CNS
- To discuss advantages and disadvantages of different imputation and analysis methods and to identify the optimal approach to offsetting bias due to subject dropout in CNS trials

#### Source of Funding: Rho

#### Literature References:

- Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? a review of published randomized controlled trials in major medical journals. *Clin Trials* 2004;1:368–76.
- Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002;7:147–77.

## FACTORS AFFECTING SUBJECT SELECTION IN CLINICAL TRIALS ACROSS CNS INDICATIONS

Jo Cara. Pendergrass, Ph.D., Clinical Psychology/Neuropsychology<sup>1</sup>, Philip Rauh, MA International Economics; BA International Relations<sup>2</sup>, Chelsea Toner, MA<sup>3</sup>, Steven D. Targum, M.D.<sup>4</sup>

<sup>1</sup>Clintara, LLC, <sup>2</sup>Clintara LLC, <sup>3</sup>Clintara, <sup>4</sup>Massachusetts General Hospital, Department of Psychiatry

**Background:** Appropriate subject selection is a critical factor that significantly affects study outcomes in clinical trials. Evidence suggests that a “dual” review process composed of site-based and site-independent assessments contributes to improved determination of subject validity and eligibility and study outcome.<sup>1</sup> Through site-independent review of screening procedures conducted as a part of the dual review process, we identified common and unique factors affecting subject selection across the CNS spectrum, including Major Depressive disorder (MDD), schizophrenia, and Alzheimer’s disease.

**Methods:** In the studies reviewed, we employed an audio-digital recording technology to record selected screen assessments for site-independent review. Study eligibility required site-independent diagnostic

verification, symptom severity confirmation, and consideration of confounding factors that might obscure ratings assessment in the trial. We employed this strategy across different CNS indications, including MDD, schizophrenia, and Alzheimer's disease. Factors influencing subject selection and enrollment for each CNS indication were identified and then compared across the different indications.

**Results:** Common factors affecting appropriate subject selection across all CNS indications included insufficient symptom severity, symptom severity too great, co-morbid psychiatric or medical diagnoses, substance abuse/dependence, unreliable/unassessable subject, unreliable/unavailable informant, insufficient interview/evaluation, and external confounding factors. Insufficient symptom severity was a common concern for subject selection in Alzheimer's disease and depression, whereas the presence of comorbid psychiatric diagnoses was a concern in schizophrenia and depression.

**Conclusions:** Site-independent review is a surveillance strategy that provides "real-time" quality assurance to improve subject validity for enrollment in clinical trials. We identified that common factors exist across several CNS indications that affect subject selection in addition to determining that certain factors were more prevalent in specific CNS indications. Identification and understanding of the type of factors affecting subject validity and eligibility can assist in characterizing study populations included and excluded from clinical trials as well as identifying study populations for inclusion in future clinical trials to maximize study outcomes.

**Learning Objectives:**

- Identify common factors affecting subject selection across different CNS indications in clinical trial research.
- Compare and contrast factors influencing subject selection that are more prevalent in certain CNS indications compared to other indications in CNS clinical trial research.

**Source of Funding:** not applicable

**Literature References:**

- Targum SD, et al. Re-defining Affective Disorders: Relevance in Drug Development. CNS Neuroscience Therapeutics 2008a; 14: 2-9.
- not applicable

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## **HOW COMMONLY USED INCLUSION AND EXCLUSION CRITERIA IN ANTIDEPRESSANT REGISTRATION TRIALS AFFECT STUDY ENROLLMENT**

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**Introduction:** In clinical trials, each specific inclusion and exclusion (I/E) criterion eliminates a percentage of the potentially eligible population from participation in the trial. Thus, each criterion incurs a cost in terms of effort and time needed to enroll the study. This paper seeks to quantify that cost by determining the percentage of the total population of patients with major depression eliminated by each of the criterion commonly used in Phase III antidepressant registration trials (ARTs).

**Methods:** To quantify the cost of each criterion, the authors did the following:

1. Determined the usual criterion used in ARTs based on a review of the 10 most recently completed trials at our institution. "Usual" was defined as being present in at least 7 of the 10 trials. The resulting list was further validated by comparing it to ART I/E criteria found in the literature.
2. Used the clinical trial population from the Sequence Treatment Alternatives to Relieve Depression (STAR\*D) trial as a surrogate for the total population of patients with non-psychotic major depression. This study was chosen for the following reasons: its large size (n = 4041), its design (i.e., more inclusive than usual ARTs), and its systematic and relevant data on each subject to this purpose.
3. Each criterion was applied to the STAR\*D population individually and then collectively. When a criterion was continuous in nature such as age or severity of depression, then the analysis was



continuous so that the effect of different “cut-points” along that continuous dimension could be assessed.

**Results:** 82% of the overall STAR\*D population would have been excluded from participating in a typical phase III ART based on all of the usual I/E criteria we selected. The effect of each I/E criterion was as follows:

1. The age range (18 – 65) excluded 14.3% of subjects
2. The lowest and most common 17-item Hamilton Depression Rating Scale cutoff of 18 excluded 15.4% of subjects
3. The requirement that the current depressive episode last at least 2 months at screening excluded 12.1% of subjects
4. The presence of an unstable general medical condition excluded 20% of subjects
5. Lack of appropriate contraception excluded 21.0% of female subjects
6. Suicidality excluded 3% of subjects
7. An Axis II condition excluded 1.7% of subjects

The effect of different cut-points on the continuous dimension items (i.e., age) will be graphically presented in the poster.

**Discussion:** These results provide those involved in clinical trial design with empirically determined data in terms of how many potential patients with major depression would need to be screened to fill an ART.

**Learning Objectives:**

- Learn how individual inclusion and exclusion criterion affect the number of patients that have to be screened to enroll a patient in a “typical” antidepressant registration using the STAR\*D population as the starting point.
- Understand how that also affects study feasibility and it’s generalizability to routine clinical practice.

**Source of Funding:** N/A

**Literature References:**

- Wisniewski SR, et al: Can Phase III Trial Results of Antidepressant Medications Be Generalized to Clinical Practice? *Am J Psychiatry* 2009; 166: 599-607.
- Posternak MA, et al: A reevaluation of the exclusion criteria used in antidepressant efficacy trials. *Am J Psychiatry* 2002; 159:191-200.

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**THE UNRELIABILITY OF RELIABILITY STATISTICS: CALCULATING INTERRATER RELIABILITY (IRR) IN CNS CLINICAL TRIALS**

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**Introduction:** Clinical trial reporting seldom includes estimates of IRR and when reported, selection of reliability statistics is often inconsistent or inappropriate. Inaccurate or inflated reliability estimates can impact study power, sample size and signal detection. A drop in reliability from .90 to .70 decreases study power from 76% to 65%. A 30% increase in sample size is required to maintain power with this decrease in reliability. Poor or inaccurate reliability can have significant consequences ranging from increased R&D costs to significant delays in getting effective drugs to patients. Guidelines are proposed for selection of appropriate reliability measures for CNS clinical trials.

**Methods:** We evaluate the appropriateness of commonly selected reliability statistics and how they are used with various types of data and methodologies, illustrating frequently misused reliability statistics that demonstrate the impact of inappropriate analytic selection on estimates of reliability.

**Results:** IRR is typically measured for diagnosis and outcome variables using 1 or both of the following methodologies: at an investigator meeting (IM) when a group of raters independently score 1 or more subject videotapes or during a trial via in-study surveillance when an expert clinician reviews and scores recorded assessments.

We propose a statistical decision tree that can be used to determine the appropriate IRR measure for various methodologies based on the type of variable, number of raters and number of subjects or observations. For example, to estimate IRR for a continuous outcome measure such as the MADRS, using IM data where a large group of raters rate two or more videotaped subjects, an intraclass correlation (ICC) should be used.

While reliability statistics require observations of more than 1 subject, it is not always possible to obtain multiple observations. We present analytic strategies that are appropriate when only one subject is rated. Common misuses of reliability statistics include using Kappa for continuous variables and treating individual scale items as independent observations when data is available from only 1 subject. Comparisons of ICC to Kappa using a 5, 10, and 20% agreement criterion demonstrate that selecting a broader criterion range for agreement can artificially inflate IRR using the same data. Results suggest ICCs calculated from a single observation by treating items as subjects may be inversely related to scale reliability. Appropriate statistics for single observations can reveal IRR issues masked by this approach.

**Discussion:** Reliability can significantly impact clinical trial outcomes. When selecting reliability statistics, researchers must consider the type of variable, number of raters, composition of the rater pool and number of observations using the guidelines presented for various methodologies.

**Learning Objectives:**

- To propose standards for estimating & reporting IRR in CNS clinical trials.
- To understand common errors in estimating IRR.

**Source of Funding:** N/A

**Literature References:**

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**SUBJECT REGISTRIES CAN REDUCE DUPLICATE SUBJECTS ENTERING CNS STUDIES**

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**Background:** Duplicate and professional clinical trial subjects are an increasingly recognized problem and likely contribute to failed CNS studies. The internet, a culture of cheating, and a dramatic increase in the complexity of studies may also contribute to rising numbers of duplicate subjects.

**Methods:** Utilizing CTSdatabase, one of 3 commercially available subject registries, 14 participating Southern California sites entered *approximately* 2,300 potential CNS clinical trial subjects who presented for prescreening between October 31<sup>st</sup> 2011 and March 31<sup>st</sup> 2013.

Prescreening subjects signed an IRB-approved Subject Database Authorization prior to being entered into the registry by site staff. Sites were immediately notified whether or not potential subjects matched with those seen at other sites.

**Results:** Of 2,300 subjects entered, 190 were same site matches (i.e. brought back to the same site at a later date) and were eliminated from the analysis. “Virtually certain” duplicates (those with a >1/10 million likelihood of matching by chance) made up approximately 7% of all prescreens. This is a sharp increase compared with the 3.45% noted when only 9 sites had entered only 1,132 subjects.

Duplicates currently (or too recently) participating in other studies or having participated in studies for exclusionary indications were prevented from entering studies.

**Conclusion:** Use of a subject registry at prescreen reduced duplicate subjects entering CNS studies. A disturbing number of duplicate subjects were found and this number more than doubled as the number of participating sites increased.

To optimize the detection and elimination of duplicate subjects from clinical trials, all sites in a given geographic area should utilize a subject database early in the screening process.

**Learning Objectives:**

- Participants can discuss the effect of increasing the number of participating sites on number of matching subjects
- Participants can identify factors that contribute to the increased recognition of duplicate and professional subjects in CNS studies.

**Source of Funding:** None.

**Literature References:**

- Shiovitz TM, Wilcox CS, Gevorgyan L, Shawkat A. CNS Sites Cooperate to Detect Duplicate Subjects with a Clinical Trial Subject Registry. *Innov Clin Neurosci*. 2013; 10(2):17-21.
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**MULTI-STATE OUTCOME ANALYSIS OF TREATMENTS (MOAT): NOVEL STATISTICAL METHODOLOGY TO ASSESS LONG-TERM OUTCOMES IN BIPOLAR ILLNESS**

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**Background:** Traditional survival analysis of time to some clinically meaningful event, e.g., relapse, intervention, discontinuation, is limited by the the lack of consideration to events that happen between time zero and the specified outcome, including subsyndromal symptoms and problems with tolerability. Realizing the limitation to this approach to assess long term efficacy in bipolar disorder (BD), we developed the Multi-state Outcome Analysis of Treatments(MOAT) methodology and used this methodology to take a fresh look at outcomes in two studies The original inspiration for this NIMH-funded methodology development project was the Quality-adjusted Time Without Symptoms or Toxicity method (QTWiST). Developed and applied in cancer chemotherapy trials, QTWiST divides total survival time into distinct periods defined by the presence or absence of symptoms or toxicity.

**Objective:** MOAT is a multi-state survival method based on Kaplan-Meier (KM) survival analysis that takes into account both measures of efficacy and tolerability, thus giving a better understanding of effectiveness of a treatment strategy. While survival analysis focuses on the occurrence and timing of predetermined clinically meaningful events, MOAT estimates the duration of time spent in these states in conjunction with other variables such as tolerability and side effects. Thus, MOAT details the quality of the time in treatment whether or not those events happen. The study employed published criteria to set cutoffs for the primary symptom states in (BD)

**Data Sources:** We used data from two FDA registration studies of lamotrigine, lithium and placebo for the purpose of methods development and results reported here. While one of the studies had enrolled recently depressed BD patients, the other enrolled manic BD patients.

**Results:** Our re-analyses of the two maintenance registration studies using this novel methodology demonstrated clinically significant findings that could not have been possible using the conventional survival analyses. In the registration study of BD patients with recent depression, MOAT revealed that although lamotrigine may “prevent mood episodes” and have longer time-to-event outcomes, most of the added time was spent with mild to moderate “subsyndromal” depressive symptoms. In the study of recently manic patients, survival analysis found that lithium was superior to placebo, but MOAT revealed that when measures of efficacy and tolerability were integrated, lithium no longer outperformed placebo.

**Importance:** Conventional survival analysis addresses questions about the timing or occurrence of events

but say nothing about the quality of the time until target events such as relapse happen, or of the experiences of the many persons who never experience the event. MOAT provides a simple way to integrate efficacy and tolerability and may more closely reflect patients' functional outcomes in maintenance studies. MOAT is a methodology that is highly adaptable to other clinical conditions and research designs. Although the development of MOAT has been in the context of BD, other chronic disorders that require maintenance treatment could apply MOAT methodologies.

#### **Learning Objectives:**

- Discuss the limitation of traditional survival analysis of time to clinically meaningful events in maintenance treatments of bipolar illness
- Discuss the utility of Multi-state Outcome Analysis of Treatments (MOAT) to fully capture the actual course of maintenance treatments in bipolar illness

**Source of Funding:** NIMH: RC1MH088431

#### **Literature References:**

- 3. Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N, DeVeaugh-Geiss J. A Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Depressed Patients With Bipolar I Disorder. *J Clin Psychiatry*; 64:1013-1024, 2003.
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### **A PRECLINICAL AND CLINICAL UPDATE ON NURELIN (ADS-5102), A NOVEL FORMULATION OF AMANTADINE HCL FOR CNS DISORDERS**

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**Background:** Amantadine, approved for the treatment of Parkinsonism, has demonstrated clinical benefit in a variety of CNS disorders, including levodopa-induced dyskinesia (LID), MS fatigue, ADHD, traumatic brain injury, and antipsychotic-induced weight gain. The mechanistic explanations for amantadine's activity are as varied as these possible uses, including NMDA receptor antagonism, dopamine release, norepinephrine release, serotonin release, BDNF upregulation and anti-cholinergic activity. Adamas is developing Nurelin, a proprietary extended release formulation of amantadine for treatment of LID in patients with Parkinson's disease (PD). Nurelin is expected to be better tolerated which may allow for higher therapeutic doses to be utilized.

**Methods:** The pharmacokinetic parameters of Nurelin were assessed in a series of pharmacokinetic studies conducted in healthy volunteers. In addition, the efficacy and tolerability of Nurelin for the treatment of LID in PD patients is currently being studied in a Phase 2/3 study entitled EASED (Extended Release Amantadine Safety and Efficacy Study in Levodopa-Induced Dyskinesia). This randomized, double blind, placebo controlled study in 80 subjects evaluated three doses of Nurelin versus placebo for the treatment of LID. Finally, to determine the potential utility of Nurelin in treating other CNS

disorders, we evaluated the efficacy of amantadine in experimental animal models of traumatic brain injury (TBI).

**Results:** Pharmacokinetic studies of Nurelin demonstrated a >50% reduction in the rate of rise of plasma concentration compared to immediate release, which enabled once a day dosing and which may result in improved tolerability. Trial design for the Phase 2/3 EASED study in LID will be discussed, and top line results are expected in June, 2013. In rodent models of TBI, treatment with clinically relevant doses of amantadine resulted in statistically significant cognitive benefit and dose-dependent increase in the number of surviving hippocampal neurons.

**Conclusions:** These results suggest that Nurelin may be a promising treatment for a variety of CNS disorders.

**Learning Objectives:**

- Recognize the applications of amantadine ER in CNS disorders
- Understand the PK/PD relationship for amantadine

**Source of Funding:** Funded by Adamas Pharmaceuticals

**Literature References:**

- Goetz CG, et al. Which Dyskinesia Scale Best Detects Treatment Response? *Mov Disord.* 2013 Feb 6. doi: 10.1002/mds.25321. [Epub ahead of print]
- Giacino JT, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med.* 2012 Mar 1;366(9):819-26.

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**JOINT PAIN AND DEPRESSIVE SYMPTOMS ASSOCIATED WITH OVARIAN SUPPRESSION: ESTROGEN AS AN INFLAMMATORY PAIN MODULATOR**

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**Background:** The prevalence of musculoskeletal pain syndromes such as osteoarthritis, fibromyalgia, systemic lupus erythematosus and rheumatoid arthritis is 2 to 10 times higher in women and compared to men. It has been noted that arthritis may be attenuated by oral contraceptive use and by pregnancy, when the estrogens are significantly higher, and may worsen after menopause. (Okifugi & Turk, 2006) A growing number of studies address the question of estrogenic modulation of inflammatory pain. Information may be indirectly obtained from trials in which estrogens or aromatase inhibitors, which deplete estrogens, are administered. Of note is that a subset of data from the Women's Health Initiative (WHI), including over 10,000 women who had hysterectomies, were randomly assigned to either estrogen or placebo. The estrogen-treated women, who were followed for seven years, were significantly less likely to have undergone any type of joint replacement. (Cirillo, et al. 2006). Women who discontinued their hormone replacement in the WHI study reported greater "pain or stiffness" compared to the placebo treated group. (Ockene, et al. 2005). Thus, it was hypothesized that women undergoing significant declines in estrogen while on GnRH agonist therapy would report an increase in joint pain as well as depressive symptoms.

**Methods:** Fifty-six premenopausal patients with endometriosis, ages 19 to 40, were evaluated at baseline, prior to GnRH agonist therapy (3.75mg IM Q 28 days), and at months 1, 2, and 5. Physical Symptoms were measured using the Menopause Symptom Index (MENSI) and the Hamilton Depression Rating Scale.

**Results:** A t-test for dependent samples indicated statistically significant increases in physical and psychiatric symptoms from baseline to: month 1 HRSD ( $t=3.89$ ,  $p<0.001$ ), MENSI ( $t=6.89$ ,  $p<0.001$ ); month 2 HRSD ( $t=4.92$ ,  $p<0.001$ ), MENSI ( $t=10.62$ ,  $p<0.001$ ); month 5 HRSD ( $t=3.96$ ,  $p<0.001$ ), MENSI ( $t=8.87$ ,  $p<0.001$ ). In particular, an item level chi-square analysis (Yates corrected) of the frequency of joint pain indicated that patients treated with GnRH agonist therapy for endometriosis reported having a significant increase joint pain at month 1 ( $X^2$  (2, N = 54) = 11.36,  $p < .001$ ); month 2 ( $X^2$  (2, N = 56) = 15.55,  $p < .001$ ); and month 5 ( $X^2$  (2, N = 44) = 5.91,  $p < .015$ ). An item level chi-square

analysis of the frequency of physical symptoms indicated that GnRH agonist patients reported having a significant increase in hot flushes, heart palpitations, headaches, sleep disturbance, numbness, and vaginal dryness, across time.

**Conclusion:** Declining ovarian steroids in women on GnRH agonist therapy are associated with increases in joint pain and depressive symptoms, as well as other physical symptoms. Evidence suggests that estrogens modulate mood as well as certain types of pain, including joint pain and arthritis. Estradiol levels are linked to changes that include: neurotransmitters, increases in bone deposition, and cytokine and immunoglobulin balance. Estrogens have complex effects on inflammatory pain which may increase the physical and mood symptoms of women.

**Learning Objectives:**

- Discuss potential effects of estrogen on the modulation of pain.
- Consider the impact of declining ovarian steroids on hormone-related mood and pain disorders.

**Source of Funding:** None.

**Literature References:**

- Craft RM: Modulation of pain by estrogens. *Pain* 2007;132:S3-S12
- Martin VT: Ovarian hormones and pain response: A review of Clinical and Basic Science Studies. *Gender Medicine* 2009;6:168-192

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**SEX DIFFERENCES IN SMOKING RISK IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER**

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Women more rapidly increase their cigarette consumption after they begin smoking and have more difficulty discontinuing their use once they become dependent. Attention-Deficit Hyperactivity Disorder (ADHD) is highly comorbid with nicotine dependence, and individuals with ADHD start smoking earlier, smoke more, and have more difficulty quitting than their non-diagnosed peers. Alterations in the dopamine reward system are implicated in both ADHD and in nicotine dependence, and ovarian hormones have been shown to affect sensitivity to both drug- and non-drug-related reward via interactions with this system. Taken together, these findings suggest that 1) the interaction of ovarian hormones with the dopamine reward system may make women with ADHD particularly vulnerable to cigarette addiction; and 2) understanding sex differences in the psychopharmacology of comorbid ADHD and nicotine dependence is an important area of unmet need in the psychopharmacology of addiction. This poster will present preliminary findings from three studies conducted in our lab that suggest that there are important sex differences in smoking outcomes in ADHD. Potential neurobiological mechanisms will be discussed. *Study 1: Sex Differences in Smoking Abstinence Effects.* In a pilot study of the effects of overnight abstinence in smokers with and without ADHD, women with ADHD demonstrated more errors of omission ( $p=.032$ ), and more errors of commission ( $p=.034$ ), in a task measuring sustained attention and inhibitory functioning, compared to men with and without ADHD, and to women without ADHD. In a follow-up investigation examining nicotine withdrawal in smokers with and without ADHD over two weeks of abstinence, at baseline females with ADHD reported increased concentration ( $p<.05$ ) and reduced irritability ( $p<.05$ ) as greater motivations for smoking compared to the other three groups. Females with ADHD also reported higher craving at baseline, and continued to report higher levels of craving during the first 3 days of a 12 day period of abstinence. Finally, on a variable ratio two-choice laboratory task designed to evaluate relative preference for “risky” versus “safe” options, females with ADHD made significantly more risky decisions at baseline ( $p<0.01$ ) and continued to make riskier choices throughout 12 days of smoking abstinence. *Study 2: Sex Differences in Time to Smoking Relapse.* Secondary analyses of two large smoking cessation trials where self-reports of ADHD symptoms were examined at baseline indicated that female smokers with high levels of self-reported ADHD symptoms lapsed significantly faster than females with low levels of ADHD symptoms, males with high levels of ADHD symptoms, or males with low levels of ADHD symptoms ( $p<.05$ ), whereas no

differences were found between male smokers with and without ADHD ( $p=.94$ ). *Study 3: Sex Differences in the Association of MAOA 30-bp Polymorphism with Initial Response to Nicotine*. Analyses of 1,900 unrelated individuals in National Longitudinal Study of Adolescent Health suggested that among those with high levels of ADHD symptomatology, the MAOA 30-bp VNTR polymorphism was differentially associated with initial response to nicotine in males and females.

#### **Learning Objectives:**

- A portion of the data presented in the poster has not been published or presented elsewhere. A portion of the data has been published previously in the following two reports and one theoretical paper:
  - McClernon, F.J., Van Voorhees, E. E., English, J., Hallyburton, M., Holdaway, A., & Kollins, S.H. (2011). Smoking withdrawal symptoms are more severe among smokers with attention deficit/hyperactivity disorder and independent of attention deficit/hyperactivity disorder symptom change: Results from a 12-day contingency managed abstinence trial. *Nicotine and Tobacco Research*, 13, 784-792.
  - Van Voorhees, E.E., Mitchell, J.T., McClernon, F.J., Beckham, J.C., & Kollins, S.H. (2012). Sex, ADHD symptoms, and smoking outcomes: An integrative model. *Medical Hypotheses*, 78, 585-593.
- Describe gender differences that have been observed in the effects of nicotine abstinence on cigarette smokers with and without ADHD.
- Identify neurobiological mechanisms relevant to both attention-deficit hyperactivity disorder (ADHD) and nicotine dependence.

#### **Literature References:**

- Bidwell, LC, Garrett, ME, McClernon, FJ, Fuemmeler, BF, Williams, RB, Ashley-Koch, AE, & Kollins, SK. (2012). A preliminary analysis of interactions between genotype, retrospective ADHD symptoms, and initial reactions to smoking in a sample of young adults. *Nicotine and Tobacco Research*, 14, 229-233.
- McClernon, F.J., Van Voorhees, E. E., English, J., Hallyburton, M., Holdaway, A., & Kollins, S.H. (2011). Smoking withdrawal symptoms are more severe among smokers with attention deficit/hyperactivity disorder and independent of attention deficit/hyperactivity disorder symptom change: Results from a 12-day contingency managed abstinence trial. *Nicotine and Tobacco Research*, 13, 784-792.
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#### **LAASDAI: LOXAPINE ADD-ON FOR ADOLESCENTS AND ADULTS WITH AUTISM SPECTRUM DISORDERS, AGGRESSION AND IRRITABILITY**

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<sup>1</sup>The Ohio State University Nisonger Center, <sup>2</sup>National Institutes of Health, <sup>3</sup>University of Kansas Cancer Center, <sup>4</sup>University of Kansas Medical Center, <sup>5</sup>University of Kansas School of Medicine, Department of Psychiatry and Behavioral Sciences, Kansas City, KS., <sup>6</sup>University of Kansas Medical Center, Kansas City, Kansas, <sup>7</sup>Department of Biostatistics, School of Medicine, UNiversity of Kansas, <sup>8</sup>Ohio State University, <sup>9</sup>NIH

*Background:* Low dose loxapine (5-15mg/day) in our experience shows promising efficacy and safety superior to the FDA-approved atypical antipsychotics risperidone (RIS) and aripiprazole (ARI) for irritability and aggression in autism spectrum disorders (ASD). Loxapine has recently been shown to produce neural sprouting in human pluripotent stem cells.

**Objective:** To study loxapine prospectively in doses of up to 15mg daily in adolescents and adults with ASD, aggression and irritability. Secondly, to measure brain derived neurotrophic factor (BDNF) as a potential biomarker of neurogenesis, controlling for platelet count and BMI. Thirdly, to measure loxapine and metabolite levels.

**Methods:** We performed a 12-week open trial of add-on loxapine in subjects aged 13 to 65 years with ASD, aggression and irritability above 14 points on the Aberrant Behavior Checklist-Irritability (ABC-I) subscale. Loxapine was added and flexibly dosed up to 15mg daily, starting with 5mg alternate days for the first 3 weeks to minimize akathisia. From weeks 1 to 6 other medications were tapered if possible, while from weeks 6 to 12 all medication doses were held stable. The primary outcome response measure was the Clinical Global Impressions scale-Improvement (CGI-I), with response defined as CGI-I of Much Improved or Very Much Improved. Secondary outcome response measures were the ABC-I, Repetitive Behavior scale-Revised, and Schalock Quality of Life scale. Serum BDNF, and loxapine and metabolite levels were assayed from samples collected at baseline and final study visit.

**Results:** Sixteen subjects were enrolled: 11 were males and 5 were females; 12 completed all 5 visits. Mean age was 21.6 years (range 13 to 39). Mean final loxapine dose was 8.4mg/day (2.5 to 15). All 14 were rated as Much Improved on CGI-I at 12 weeks (100%). Percent change in ABC-I was -31%,  $p=0.01$ . Mean BMI did not increase significantly. Side effects were minimal. Prolactin elevation did not occur. BDNF levels measured in a small subgroup of 11 subjects, increased significantly,  $p=0.04$ .

**Learning Objectives:**

- To discuss weight gain and metabolic and associated medical side effects of atypical antipsychotics as they occur in adolescents and adults with autism spectrum disorders (ASD).
- To discuss loxapine potential for aggression and irritability in adolescents and adults with ASD, and loxapine neurotrophic effects and impact on BDNF.

**Source of Funding:** University of Kansas Medical Center, Internal funding.

**Literature References:**

- Hellings, J.A., Zarcone, J.R., Crandall, K., Wallace, D., Schroeder, S.R. (2001). Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism. *J Child Adolesc Psychopharm* 11, 229-238.
- Brennan KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S, et al. (2011). Modelling schizophrenia using human induced pluripotent stem cells. *Nature*. 473 (7346):221-5.

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**SELF-REPORT NEUROSCIENCE RATING SCALE GUIDES RATIONAL PSYCHOPHARMACOLOGY TO DOCUMENT COGNITIVE IMPROVEMENT IN 121 OUTPATIENT MENTAL HEALTH CENTER INDIVIDUALS**

David R. Torres, Board Certified by the American Society of Psychopharmacology<sup>1</sup>

<sup>1</sup>Advanced Clinical Psychopharmacology

Self-report Neuroscience Rating Scale Guides Rational Psychopharmacology to Document Cognitive Improvement in 121 Outpatient Mental Health Center Individuals.

**Background:** In Colorado, there is a movement to replace civil state hospital beds allocated for mental health center use with individuals undergoing forensic competency evaluations. This movement has led to a lack of available psychiatric beds at the state level increasing the need for rapid psychopharmacologic stabilization of individuals in emergency rooms and mental health centers. Innovative evidenced based treatment algorithms driven by self report scales utilizing electronic health records are necessary for optimal treatment of severe neuropsychiatric illness.

**Methods:** Rapid pharmacologic assessment and treatment are part art and part science. Innovations of previously established treatment protocols are necessary to provide optimal care. A neuropsychiatric scale designed in 2009 called the Colorado Cycling Mood Rating Scale (CMRS) used to assess and guide medication management of mentally ill individuals seen in a mental health center system in the frontier areas of Southeastern Colorado has shown positive results in its first 5 months of implementation. The CMRS combines select questions from the Young Mania Rating Scale, the Hamilton Depression Scale,



the Adult Attention Deficit Disorder Self Report Scale and questions related to mood stabilizer toxicity. Each of these validated scales have strengths, however, a global assessment of thought, behavior and functioning is necessary before psychopharmacologic recommendations can be made. The self rating scale is 60 questions long and takes 3 minutes to fill out and needs corroboration from a third party. The goals of treatment were to have all individuals enter remission rapidly and treat co-morbid illness including vasomotor symptoms, pain, potential seizure activity and substance abuse concurrently. Treatment was initiated without the use of benzodiazepines, anticholinergics or opiates to preserve cognitive functioning.

**Results:** The use of a universal neuropsychiatric screen to assess and guide medication management resulted in improvement from baseline of 10 to 50%. Almost all individuals were treated to remission. Most of the improvement seen was in those individuals with depressive symptoms. Those individuals who were treated with stimulants and wake promoters showed benefit in the realms of attention, concentration and focus. Statistically significant improvement was shown in level of functioning, memory, attention, concentration and executive functioning at the 0.5 level of confidence. The Colorado Cycling Mood Rating Scale provides guidance regarding percentile dose reductions of mood stabilizers when side effects are present. The scale has clinical utility when used in consultation with primary care offices and emergency rooms, when recommendations regarding medication management are required. The scale guides medication management when one time test dosing of atypical antipsychotics and stimulants are used. The scale enables rapid psychopharmacologic assessment and treatment of mentally ill individuals and documents cognitive improvement in the electronic medical record.

**Learning Objectives:**

- Learn to use self-report composite validated mood and cognition scale to guide medication management
- Learn to use electronic medical record to document cognitive improvement in a mental health center population

**Source of Funding:** No Funding

**Literature References:**

- Performance and interview-based assessments of cognitive change in a randomized double-blind comparison of lurasidone vs. ziprasidone Schizo Res. Apr;127(1-3):188-94. Epub 2011 Jan 31
- Evaluation of functionally meaningful measure for clinical trials of cognition enhancement in schizophrenia Am J Psychiatry. 2011 Apr;168(4):400-7. Epub 2011 Feb 1.

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**LEVOMILNACIPRAN SR AND FUNCTIONAL EFFICACY IN MAJOR DEPRESSIVE DISORDER: A POOLED ANALYSES OF 5 DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS**

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**Objective:** Major depressive disorder (MDD) is associated with functional impairment across work, social, and family domains. Improved functioning is a critical component of recovery in patients with MDD. Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with approximately 2-fold greater potency for reuptake inhibition of norepinephrine than serotonin. Levomilnacipran is in late-stage clinical development for the treatment of major depressive disorder (MDD) in adults; a sustained release (SR) formulation was developed for once-daily dosing. Data from 5 short-term studies (NCT00969709, NCT01377194, NCT00969150, NCT01034462, EudraCT:2006-002404-34) of levomilnacipran SR in adults were used to evaluate functional improvement associated with MDD.

**Methods:** Data from 2 fixed-dose (40, 80, and 120 mg/d; 40 and 80 mg/d) and 3 flexible-dose (40-120 mg/d [2 studies]; 75-100 mg/d) 8-10 week, randomized, double-blind, placebo-controlled trials evaluating levomilnacipran SR 40-120 mg/day were analyzed. Patients were 18-78 years of age and met DSM-IV-

TR criteria for MDD. In all studies, improvement in functional disability was measured by change from baseline to endpoint in Sheehan Disability Scale (SDS) total score; analysis was based on the modified Intent-to-Treat (ITT) Population using the mixed-effects model for repeated measures (MMRM) approach. Post hoc analyses of SDS data examined treatment differences in the overall pooled population and subgroups (age, sex) at Week 8; overall functional remission (SDS total score  $\leq 6$  and subscale scores  $\leq 2$ ) was also analyzed.

**Results:** The pooled ITT Population consisted of all patients who had received  $\geq 1$  dose of study drug and had a postbaseline Montgomery-Åsberg Depression Rating Scale assessment (levomilnacipran SR=1566; placebo=1032). In individual studies, least squares mean difference (LSMD) in SDS total score change from baseline to Week 8 for levomilnacipran SR vs placebo was significantly greater in both fixed-dose studies (-2.2 and -2.3;  $P \leq .01$ ) and 2 flexible-dose studies (-2.7 and -2.6;  $P < .001$ ); the difference was not significant in 1 flexible-dose study (-0.5;  $P = .562$ ). In the overall pooled population, the LSMD (95% CI) in SDS total score change from baseline to Week 8 was statistically significant for levomilnacipran SR vs placebo (-2.1 [-2.8, -1.4];  $P < .0001$ ); remission rates were also significantly higher for levomilnacipran SR (26%) vs placebo (20%;  $P = .0001$ ). In analyzed subsets, SDS improvement was statistically significant for levomilnacipran SR vs placebo in men (-2.4 [-3.5, -1.2],  $P = .0001$ ) and women (-1.9 [-2.7, -1.0];  $P < .0001$ ), and younger (18-55 years: -1.9 [-2.6, -1.1],  $P < .0001$ ) and older ( $\geq 55$  years: -3.0 [-4.5, -1.4],  $P = .0003$ ) patients.

**Conclusions:** In pooled analyses of 5 placebo-controlled trials, statistically significant differences in functional improvement were seen in favor of levomilnacipran SR patients compared with placebo. Treatment differences in SDS scores and SDS remission rates demonstrate that levomilnacipran SR treatment decreased functional impairment associated with MDD.

**Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the effect of levomilnacipran SR versus placebo on SDS measures in patients with major depressive disorder.
- At the conclusion of this session, the participant should be able to discuss functional improvement in different patients subgroups treated with levomilnacipran SR compared with placebo.

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

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**DESVENLAFAXINE 50- AND 100-MG/D VS PLACEBO FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A PHASE 4, RANDOMIZED CONTROLLED TRIAL**

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**Background:** The objective was to assess the short-term efficacy and safety of desvenlafaxine 50 and 100 mg/d (administered as desvenlafaxine succinate) vs placebo for treating major depressive disorder (MDD). Because some antidepressants are associated with treatment-emergent sexual dysfunction (1), assessment of sexual function was a secondary objective.

**Methods:** Adult outpatients ( $\geq 18$  years) who met DSM-IV-TR criteria for MDD and had screening and baseline 17-item Hamilton Depression Rating Scale (HAM-D<sub>17</sub>) total scores  $\geq 20$  were randomly assigned to receive placebo or desvenlafaxine (50 or 100 mg/d) in an 8-week, fixed-dose trial, with a 1-week titration and taper for the 100 mg dose. The primary efficacy end point was change from baseline in HAM-D<sub>17</sub> total score at week 8, analyzed using a mixed-effects model for repeated measures. Sexual function was assessed using the Arizona Sexual Experiences Scale (ASEX), a validated outcome measure, analyzed using analysis of covariance; the treatment by gender interaction was tested in a preliminary model to determine whether ASEX results should be presented separately by gender.

**Results:** The safety population ( $\geq 1$  dose of study drug) included 909 patients, and the intent-to-treat population (baseline and  $\geq 1$  postbaseline HAM-D<sub>17</sub> evaluation) included 886 patients (placebo, n=294; desvenlafaxine 50 mg, n=291; desvenlafaxine 100 mg, n=301). A total of 422/909 (46%) patients were sexually active at baseline and at  $\geq 1$  postbaseline time point and were included in the ASEX analysis. There was a significantly greater decrease in adjusted mean HAM-D<sub>17</sub> total score from baseline to week 8 for desvenlafaxine 50 mg/d ( $-11.28$ ;  $P=0.006$ ) and desvenlafaxine 100 mg/d ( $-11.67$ ;  $P=0.001$ ) compared with placebo ( $-9.71$ ) after adjusting for multiplicity. In the ASEX analysis, the treatment by gender interaction was not significant. All  $P$ -values for desvenlafaxine vs placebo comparisons were  $>0.05$  for ASEX total score (adjusted mean difference vs placebo [95% CI]: desvenlafaxine 50 mg/d,  $-0.09$  [ $-0.98$ ,  $0.80$ ]; desvenlafaxine 100 mg/d,  $-0.32$  [ $-1.19$ ,  $0.55$ ]) and all item scores, with no adjustment for multiplicity. Rates of discontinuation due to adverse events were 3.3% and 5.2% for desvenlafaxine 50 and 100 mg/d, respectively (placebo, 2.3%).

**Conclusions:** These results support previous findings demonstrating antidepressant efficacy, safety, and tolerability of desvenlafaxine 50 and 100 mg/d vs placebo (2). Although the study was powered for efficacy and not sexual function, ASEX scores were comparable between desvenlafaxine and placebo.

#### **Learning Objectives:**

- To recognize that desvenlafaxine 50- and 100-mg doses are effective in treating patients with MDD.
- To explain that no differences from placebo were observed in ASEX scores for either desvenlafaxine dose.

**Source of Funding:** This study was sponsored by Pfizer.

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## **THE CLINICAL DECISION TO EXTEND CITALOPRAM THERAPY: DISTINGUISHING LATE REMITTERS AND NON-REMITTERS IN LEVEL 1 OF STAR\*D**

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**Background:** Clinicians often face a decision about the course of treatment for patients who do not respond to an antidepressant within 4-6 weeks. Some patients show delayed remissions to

antidepressants. We hypothesized that there are important differences between patients who remit late in an antidepressant trial and those who do not remit.

**Methods:** We compared clinical and demographic characteristics in late remitters and ultimate non-remitters using chi-square tests for categorical variables and t-tests for continuous variables. A logistic regression model was constructed to show how those variables may predict a subject being a late-remitter or ultimate non-remitter.

**Results:** Compared to ultimate non-remitters, late remitters were shown to have better social functioning after 6 weeks of treatment as measured by the Work and Social Adjustment Scale ( $P < .001$ ; Cohen's  $d = 0.7$ ), a greater degree of improvement on the QIDS-SR during the first six weeks of treatment ( $P < .001$ ; Cohen's  $d = 0.44$ ). Late remitters also had milder depression and better social functioning at baseline but the effect sizes were smaller. Based on our multiple logistic regression model, those who showed greater improvement in depressive symptoms on the QIDS-SR from week 0 to 6 were more likely to be ultimate remitters (OR = 1.095; 95% CI: 1.068-1.124;  $p < .001$ ). Similarly, those with less impairment on the Q-LES-Q were more likely to eventually remit (OR = 1.016; 95% CI: 1.006-1.026;  $p = .001$ ) as were those with better health as measured by SF12 physical component at baseline (OR = 1.018; 95% CI: 1.006-1.030;  $p = .002$ ).

**Conclusions:** A significant minority of participants (27%) achieved criteria for remission late in the course of an antidepressant trial. Improvement of depressive symptoms short of remission and better work and social function at week 6 were mediators for ultimate remission. These results have high ecological validity.

**Learning Objectives:**

- Describe the variation in time-course response of depressed patients to an antidepressant.
- Described differences between late remitters and non-remitters to citalopram in STAR\*D.

**Source of Funding:** This work was supported by a grant that the Pritzker Neuropsychiatric Disorders Research Consortium has made to the Department of Psychiatry at Weill Cornell Medical College. Grant number NA.

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**LISDEXAMFETAMINE DIMESYLATE AUGMENTATION IN MAJOR DEPRESSIVE DISORDER: POST HOC ITEM ANALYSIS OF RESIDUAL SYMPTOMS ON THE QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY SELF-REPORT IN CLINICIAN-RATED NONREMITTERS AND REMITTERS**

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**Purpose:** In a double-blind, placebo (PBO)-controlled trial, lisdexamfetamine dimesylate (LDX) augmentation of escitalopram improved depressive symptoms on the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) in adults with major depressive disorder (MDD). Post hoc QIDS-SR item analyses were conducted to understand specific symptom changes with LDX augmentation.

**Methods:** Adults with nonpsychotic MDD and residual depressive symptoms (HAM-D17 score  $\geq 4$ ) after 8 weeks of open-label escitalopram (wk 1: 10 mg/d; 20 mg/d thereafter) were randomized to 6 weeks of LDX (20–50 mg/d) or PBO augmentation. Post-hoc QIDS-SR item analyses are presented descriptively in nonremitters (PBO, n=64; LDX n=65) and remitters (PBO, n=21; LDX, n=23) (augmentation baseline MADRS total score  $>10$  and  $\leq 10$ , respectively); the study was not powered to comparatively assess these endpoints.

**Results:** In nonremitters, least squares mean (90% CI) treatment differences (LDX–PBO) favored LDX (prespecified critical  $\alpha=0.10$ ) for MADRS ( $-2.3 [-4.5, -0.1]$ ,  $P=0.0902$ ) and QIDS-SR ( $-1.2 [-2.2, -0.1]$ ,  $P=0.0774$ ) total score at end of study. The numerically highest mean $\pm$ SE QIDS-SR item score (range, 0–3) at augmentation baseline was reduced sleeping during the night (PBO,  $1.69\pm 0.128$ ; LDX,  $1.82\pm 0.118$ ) in nonremitters and increased weight (PBO,  $1.20\pm 0.374$ ; LDX,  $1.33\pm 0.167$ ) in remitters. Mean treatment differences with 90% CIs not crossing 0 in nonremitters at week 14 favored LDX for sleeping too much ( $-0.37 [-0.594, -0.155]$ ; PBO [n=62], LDX [n=63]), feeling sad ( $-0.35 [-0.607, -0.095]$ ; PBO [n=62], LDX [n=63]), increased appetite ( $-0.46 [-0.843, -0.072]$ ; PBO [n=28], LDX [n=15]), energy level ( $-0.29 [-0.567, -0.006]$ ; PBO [n=62], LDX [n=63]), and feeling restless ( $-0.35 [-0.574, -0.121]$ ; PBO [n=62], LDX [n=63]). In remitters, week 14 mean (90% CI) treatment differences for decreased appetite ( $0.34 [0.054, 0.621]$ ; PBO [n=11], LDX [n=21]) and decreased weight ( $0.39 [0.010, 0.766]$ ; PBO [n=10], LDX [n=17]) favored PBO; view of myself ( $-0.29 [-0.543, -0.029]$ ; PBO [n=21], LDX [n=22]), general interest ( $-0.29 [-0.509, -0.067]$ ; PBO [n=21], LDX [n=22]), and energy level ( $-0.48 [-0.738, -0.232]$ ; PBO [n=21], LDX [n=22]) favored LDX.

**Conclusions:** Nonremitted and remitted individuals with MDD showed different residual symptom patterns; LDX augmentation appeared to improve distinct symptoms in nonremitters and remitters. These data should be interpreted cautiously due to small sample size.

#### **Learning Objectives:**

- Understand residual depressive symptoms in antidepressant monotherapy remitters and nonremitters
- Describe LDX augmentation effects on depressive symptoms measured by individual QIDS-SR items

**Source of Funding:** Shire Development LLC

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### **OPEN-LABEL, FLEXIBLE-DOSE REPEATED INTRAVENOUS KETAMINE INFUSIONS AS ADJUNCT IN OUTPATIENTS WITH TREATMENT RESISTANT MAJOR DEPRESSION WITH SUICIDAL IDEATION**

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We investigated the feasibility and efficacy of open-label repeated intravenous administration of ketamine in severely depressed, treatment-resistant, chronically suicidal outpatients.

**Methods:** Patients were referred by their treating psychiatrist. Inclusion criteria were primary diagnosis of MDD (DSM-IV), no history of psychotic features, age 18-65 years, Hamilton Depression Rating Scale

28-Items (HAM-D 28) score  $\geq 20$ , history of 3 or more failed treatments during the current episode, endorsing suicidal ideation (SI) for more than 3 months per the Columbia-Suicide Severity Rating Scale (CSSRS) and have a HAM-D suicide item score  $\geq 2$  (current SI, thoughts of own death), on antidepressant regimen stable for 4 weeks.

After a two week lead-in, patients received 6 infusions of ketamine over 3 weeks followed by a 3-month phase of visits every other week. The dose was 0.5 mg/kg, over 45 minutes. If the participant did not experience an improvement  $\geq 30\%$  in HAM-D score after the 3rd infusion, the dose was increased to 0.75 mg/kg for infusions 4-6.

Response was defined as 50% improvement on the HAM-D score from screen to the 6<sup>th</sup> infusion, remission as total HAMD score  $\leq 7$ . Clinician Administered Dissociative States Scale (CADSS) was administered at time points 0, 60, 120 minutes of every infusion. Side effects and vital signs were monitored during the infusion and for 3 hours afterwards.

**Results:** To date, 12 subjects were screened and 10 were enrolled in the study (9F/1M, age  $51.3 \pm 6.7$ ). 7/10 had one or more comorbid anxiety disorders. The mean HAM-D score at screening was  $28.2 \pm 3.3$ . Subjects were taking an average of  $2 \pm 0.8$  antidepressants and  $1.9 \pm 1.5$  other psychotropic medications. On average, subjects had failed  $8.6 \pm 5.2$  previous medication trials in the current depressive episode. After the 3rd infusion only one patient improved by 30%. After the 6<sup>th</sup> infusion, 4/10 patients met criteria for response and 2/10 met criteria for remission. All 10 subjects had significant suicidal ideation at the start of the trial, and after the last infusion 5/10 had no ideation over the previous week.

**Tolerability:** The patients experienced minimal sedation and mild dissociative symptoms during the infusions,  $2.6 \pm 2.0$  on the CADSS at T60 and  $0.2 \pm 0.4$  at T120. Out of the ten participants, one discontinued enrollment after the second infusion, and five dropped out during follow up (this did not seem to be correlated with response). Vital signs showed mild increase in systolic blood pressure during the infusion (highest increase 51mmHg; mean  $15.8 \pm 13.5$ mmHg).

**3-month follow up:** none of the subjects sustained the response at 2 weeks, one of the patients who was not responder continued to improve and approached response. In one subject SI remained significantly lower than screening, while the subjects who relapsed returned to the initial severity.

**Discussion:** Ketamine infusions in outpatients with TRD was feasible and well tolerated. Overall efficacy seems to be lower and delayed compared to published samples, and this could be due to interactions with concurrent medications or to increased level of resistance.

The study of long term strategies to sustain ketamine efficacy is necessary.

#### **Learning Objectives:**

- feasibility of open-label repeated intravenous ketamine as adjunct in TRD
- use of ketamine in outpatient setting
- safety and efficacy of ketamine in patients with chronic suicidal ideation

**Source of Funding:** Supported by Grant 1 UL1 RR025758, UL1 TR000170-05, Harvard Clinical and Translational Science Center, from the National Center for Advancing Translational Science" and departmental funds.

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Failed and negative results are a common problem in clinical trials with antidepressant medications. It is well known that higher than anticipated placebo response is one major factor affecting these study outcomes.

Band-pass filter analysis is a novel methodology based on signal detection theory that seeks to control excessively high or low placebo response levels. This strategy is based on the identification of non-plausible placebo response trajectories in a given recruitment center. An optimization of the signal-to-noise ratio is obtained by identifying the cut-off values located at the high and low ends of the placebo response distribution curve and then filtering-out the values falling outside these boundaries.

The CX157-201 (TriRima) trial was a randomized, double-blind, placebo-controlled study of the efficacy, safety and tolerability of CX157 in subjects with treatment resistant depression (TRD). 29 US centers enrolled 360 patients assigned equally to TriRima or placebo. The primary endpoint (The Montgomery-Asberg Depression Rating Scale, MADRS) failed to separate CX157 from placebo and the outcome was considered a negative or failed trial.

A band-pass filter analysis was performed on the MADRS clinical scores in a post-hoc analysis. This analysis excluded trial sites with excessively high placebo response and revealed that the data from these few sites were directly associated with the trial failure. Alternatively, trial sites that had placebo MADRS score reductions from baseline to week 6 between a low of 3 and a high of 7-10 points revealed a strong, significant signal between TriRima and placebo. In addition, the results of the re-analysis of the evaluable population showed that there was a substantial improvement in the treatment effect when the band-pass filter is applied. Further, the percentage of responders was significantly higher in TriRima treated than placebo patients when these band-pass filters were applied. However, the linear mixed-effects modeling approach for repeated measures (MMRM) for the MADRS was still unable to detect a statistically significant difference between TriRima and placebo after applying the band-pass filter approach. These post-hoc findings suggest that TriRima may indeed have antidepressant activity despite the failed trial. These findings also draw attention to the issues of site and subject selection in clinical trials and demonstrate that every trial site is not the same. Finally, these findings suggest that further studies applying the band-pass filter analysis are warranted.

#### **Learning Objectives:**

- Novel Method for assessing efficacy in Psychiatric RCTs
- Challenges and issues in conducting MDD trials

**Source of Funding:** Funded entirely by CeNeRx BioPharma, Inc

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### **INTERFERON-ALPHA-INDUCED BEHAVIORAL CHANGES CORRELATE WITH INCREASED CNS GLUTAMATE WHICH IN TURN IS ASSOCIATED WITH ACTIVATION OF THE KYNURENINE PATHWAY**

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**Background:** Peripheral inflammatory states and their behavioral consequences including depression and fatigue have been well documented.(1) One mechanism that may contribute to inflammation-induced behavioral changes is alterations in central nervous system (CNS) glutamate metabolism secondary to activation of the kynurenine (KYN) pathway. Indeed, end products of KYN pathway activation including

quinolinic acid (QUIN) have been shown to activate NMDA receptors, which can stimulate glutamate release.

**Methods:** To examine the role of CNS glutamate and the KYN pathway in inflammation-induced depression and fatigue, proton magnetic resonance spectroscopy (MRS) was conducted in 12 patients with hepatitis C virus (HCV) before and after 4 weeks of treatment with interferon (IFN)-alpha compared to 12 HCV patients awaiting IFN-alpha therapy. IFN-alpha is an inflammatory cytokine well known to induce symptoms of depression and fatigue in association with increases in plasma KYN and cerebrospinal concentrations of KYN and QUIN.

**Results:** Compared to controls, the glutamate/creatine ratio in the left basal ganglia significantly increased following 4 weeks of IFN-alpha administration ( $p < 0.05$ ), which in turn significantly correlated with increases in fatigue ( $r = 0.44$ ,  $p < 0.05$ ). Interestingly, increases in the left basal ganglia glutamate/creatine ratio was also correlated with plasma concentrations of the KYN pathway metabolite, 3-OH anthranilic acid, which is the metabolite immediately upstream of QUIN ( $r = 0.61$ ,  $p < 0.005$ ).

**Conclusions:** These data are consistent with previously reported alterations in basal ganglia function following IFN-alpha administration and suggest that IFN-alpha activation of the KYN pathway may lead to changes in CNS glutamate metabolism which in turn are associated with IFN-alpha-induced behavioral changes including fatigue. (2)

**Learning Objectives:**

- 1. To better understand neuroimmune hypothesis of Major Depression
- 2. To better understand biomarker tracking using magnetic resonance spectroscopy

**Source of Funding:**

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Biomedical Imaging Technology Center of Emory University.

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**EFFECT OF L-METHYLFOLATE ON GENETIC MARKERS ASSOCIATED WITH MONOAMINE IMBALANCE FROM A RANDOMIZED CLINICAL TRIAL OF PATIENTS WITH MAJOR DEPRESSION: A POST HOC ANALYSIS**

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**Background:** An association is reported between monoamine imbalance and the risk of MDD and antidepressant response. The response to L-methylfolate 15 mg as an adjunct to SSRIs was examined when stratified by baseline levels of genetic markers associated with monoamine dysregulation.

**Methods:** 75 inadequate responders to SSRIs were enrolled in a 60-day, multi-center, double-blind, placebo-controlled trial. Patients received L-methylfolate 15 mg/day for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/day for 30 days, or placebo for 60 days. In a post hoc analysis, mean



change from baseline to endpoint was evaluated for L-methylfolate and placebo according to the baseline presence genetic markers.

**Results:** 74 patients were enrolled. For pooled data, the response rate on the HDRS-17 with adjunctive L-methylfolate 15 mg/day vs. SSRI therapy plus placebo was 17.7% ( $p=0.04$ ). Pooled differences in mean change on HDRS-17 and HDRS-28 were significantly different ( $p=0.05$  and  $p=0.02$ , respectively). Greater mean changes from baseline on the HDRS-28 were observed with L-methylfolate vs. placebo for mutation biomarkers including FOLH1, GCH1, GCHFR, MTHFR, RCF1 & RCF2, CACNA1C, COMT, DNMT3B, DRD2, and MTR. No treatment effect was associated with L-methylfolate in mutation-negative (wild-type) patients.

**Conclusions:** A robust response was observed with L-methylfolate as an adjunct to SSRIs. In this post hoc analysis, the presence of genetic markers at baseline was associated with a robust response, but a priori replication in larger cohorts is needed.

#### **Learning Objectives:**

- Recognize that addressing underlying metabolic dysfunction may result in improvement of symptoms of depression.
- Identify the effect of antidepressant treatment on symptoms of depression, and in patients with baseline alternations in genetic or biological markers.

**Source of Funding:** This work was funded by research grants from PamLab Inc., Covington, Louisiana

#### **Literature References:**

- Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M. L-methylfolate as adjunctive therapy for SSRI-resistant major depressive disorder: results of two randomized, double-blind, parallel-sequential trials. *Am J Psychiatry*. 2012;169:1267-74.
- Stahl SM. Methylated spirits: epigenetic hypotheses of psychiatric disorders. *CNS Spectr*. 2010;15:220-30.

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## **THE USE OF ANTIDEPRESSANTS IN PAINFUL RHEUMATOLOGICAL CONDITIONS: A SYSTEMIC REVIEW**

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**Background:** Pain is one of the main symptoms of rheumatological conditions. Standard analgesics (NSAIDs, opioids) can be ineffective in some cases. It is well known that many patients with pain have co-morbid psychiatric conditions. Nevertheless, antidepressants can be very useful as analgesics even in absence of depression independent of antidepressive effects. The results obtained with antidepressants are highly variable and their use as analgesics remains controversial.

**Objective:** The aim of this study is to review the evidence supporting the use of anti-depressants in painful rheumatological conditions.

**Methods/Data Collection:** Different databases including PubMed, Medline, Ebsco, and Cochrane library were searched for relevant articles. Inclusion criteria included all classes of anti-depressants and patients with rheumatic conditions including fibromyalgia, rheumatoid arthritis (RA), osteoarthritis (OA) and ankylosing spondylitis (AS) with no other medical comorbidities, which can cause pain. 48 studies were identified for review.

**Results:** Anti-depressants have clear analgesic effects in fibromyalgia, but they have weak analgesic effects in AS/low back pain. Anti-depressants have little evidence supporting their use in RA/OA (8 studies for RA and 4 studies for OA). TCA is the best-studied and proven class of anti-depressants as analgesics, (31 studies), especially for fibromyalgia (also SNRI). Antidepressants can be used as adjunct analgesics.

**Conclusion:** We believe that antidepressant drugs are beneficial, even in the absence of depression, suggests that these drugs could have intrinsic analgesic activity independent of their antidepressive

effects. Antidepressant drugs may be useful in painful rheumatologic conditions, but in some studies the analgesic effects of antidepressants may be associated with functional impairment, sleep disorders, and fatigue. Further studies are required to determine antidepressants' analgesic mechanism of action and the specific role they should play in the management of chronic painful rheumatologic conditions.

**Learning Objectives:**

- The aim of this study is to review the evidence supporting the use of anti-depressants in painful rheumatological conditions
- Secondary aim is to review which classes of antidepressants can work as analgesics in rheumatological conditions

**Source of Funding:** None

**Literature References:**

- Comment on: Is there any evidence to support the use of anti-depressants in painful rheumatological conditions? Systematic review of pharmacological and clinical studies & Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy
- Anti-depressants as analgesics: A systemic review; M E Lynch; J Psychiatry Neurosci; 2001 January; 26(1); 30-36

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**IS THERE BIAS IN ATTENTION BIAS? A METHOD STUDY OF A NEW SURROGATE MARKER FOR DEPRESSION**

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**Background:** Depression research is challenged by the subjectivity of its primary outcome measures, which are invariably based on self-report of symptom severity. In the search for surrogate markers that may reliably measure treatment response without the added risks of inflation and expectancy, cognitive bias has emerged as one candidate. Depressed and dysphoric individuals exhibit attentional bias towards negative stimuli, a factor in the onset and maintenance of depression. Recent studies also suggest that bias may improve with both pharmacological and cognitive intervention. As general awareness of this field of research grows, it will be critical to understand the extent to which measurable bias can be consciously controlled, and whether it too is vulnerable to suggestion and expectancy.

**Method:** As part of an ongoing study, participants (all-comers) were recruited from a university subject pool and underwent a dot probe task to examine reaction time (ms) for emotional face relative to neutral face stimuli (i.e., bias). The dot probe was modeled on tasks employed in published depression studies to date. Two faces (emotional and neutral) simultaneously appear on the screen for 1000 ms followed by a target in either the same or different location as the emotional face. The participant must make a simple decision about the target and respond with a keystroke for 96 trials. In this study, the same task was repeated three times under different explicit instruction sets 1) standard instructions, 2) directive instruction to avoid negative stimuli, or 3) directive instruction to attend to negative stimuli. In addition, subjects completed the Center for Epidemiological Studies Depression Scale (CES-D). We hypothesized that bias scores would differ significantly between instruction condition, and under the assumption that depression reduces cognitive control, that symptom severity would significantly moderate the effect of instruction.

**Results:** In this non-clinical sample (N=41), mean bias scores in the standard instruction condition were close to 0 (sad:  $-0.97 \pm 42.14$ ; happy:  $-6.98 \pm 36.71$ ); mean CESD score was  $12.66 \pm 11.04$ . Bias differed significantly between instruction conditions for both sad faces [ $F(1.67, 66.65) = 73.34, p < 0.0005$ ] and happy faces [ $F(1.43, 57.41) = 65.66, p < 0.0005$ ]. In addition, CESD scores significantly moderated bias in the attend condition, i.e., participants with higher symptom levels were less able to control the direction of their attention than participants with lower symptom levels ( $p < 0.05$ ).

**Conclusions:** In a standard dot probe paradigm, attention bias was easily manipulated through minor alterations in the instruction set. All participants, though to a lesser extent dysphoric participants, were

able to control the direction of their attention even in the context of rapid stimuli presentation. Researchers should take caution that seemingly objective surrogates may in fact present the same risks to trial integrity as symptom scales. Future research will examine the extent to which reductions in stimuli speed affect controllability of response, and will investigate alternate forms of bias measurement (e.g., eye gaze tracking) that may be less vulnerable to suggestion.

**Learning Objectives:**

- To understand the extent to which attention can be controlled in dot probe paradigms
- To better appreciate the vulnerabilities of surrogate markers in depression research

**Source of Funding:** University seed funds

**Literature References:**

- Harmer CJ. Emotional Processing and Antidepressant Action. Current topics in behavioral neurosciences. 2012 May 8 [Epub ahead of print].
- Joormann J, Gotlib IH. Selective attention to emotional faces following recovery from depression. J Abnorm Psychol. 2007 Feb;116(1):80–5.

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**DESCRIPTIVE STUDY OF PATIENTS TREATED WITH SELEGILINE TRANSDERMAL SYSTEM (STS) AT THE DEPARTMENT OF VETERAN AFFAIRS**

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**Background:** Currently one in six people experience a depressive episode in their lifetime, but only 50% of those seek treatment. The American Psychiatric Association (APA) has recommended MAOIs as potentially beneficial for patients with atypical depression and for those that have failed to see improvement on other antidepressants. In 2006, the FDA approved the use of selegiline (an MAOI) as a transdermal patch for the treatment of depression in adults. The majority of research that has been conducted on patients treated with selegiline transdermal system (STS) was completed in 2008 or earlier covering less than two years after FDA approval. This study looked to identify and describe patients treated with selegiline transdermal system in the Department of Veterans Affairs (VA).

**Methods:** Patients with at least one prescription/medication record for STS between 1/1/2006-7/31/2012 and at least 180 days of baseline healthcare coverage in the VA system (defined as a visit, medication, lab or procedure that happened 180 days or more prior to index date) were included in the study. The index date was defined as the first documented STS record. Descriptive statistics, including age, gender, race, BMI, and index year, were determined. Documented diagnoses (using ICD-9 codes) and medications were explored in the 180 days before and after the index date.

**Results:** 818 patients were found with at least one prescription for STS in the study period. Of those, 719 patients (16% females, mean age 54.8 years SD 13.3, 36% BMI 25.0-29.9, 41% BMI ≥ 30.0) had at least 180-day baseline health coverage. 76% of patients had a documented diagnosis for Major Depressive Disorder (MDD) in the 180 days after and including the index date. 39% had a documented diagnosis for PTSD, 37% for Anxiety, 15% for Bipolar Disorder, 9% for Personality Disorder, and 5% for Parkinson Disease, during the same time period. The majority of patients, 630 (88%), were treated with 6 mg/24 hr STS compared to the 9 mg, 192 (27%), and 12 mg, 79 (11%), doses in the 180 days after and including the index date. In addition, 165 (23%) patients also had a prescription for another MDD treatment, 324 (45%) for a Bipolar Disorder treatment, 44 (6%) for a Parkinson's Disease treatment, and 9 (1%) for a Alzheimer's Disease treatment in the same time period.

**Conclusion:** Although indicated for MDD, only 76% of patients treated with STS had a documented diagnosis for MDD after starting STS treatment. Diagnosis and treatment for other related conditions was seen among these patients. This patient population will be furthered studied in terms of change in treatment patterns, change in weight/BMI, and rates of specific short-term/long-term outcomes of interest.

**Learning Objectives:**

- Identify patients treated with selegiline transdermal system in the Department of Veterans Affairs

- Describe the characteristics of patients treated with selegiline transdermal system in the Department of Veterans Affairs

**Source of Funding:** This study was funded by Mylan Specialty L.P.

**Literature References:**

- Thase ME. The role of monoamine oxidase inhibitors in depression treatment guidelines. *J Clin Psychiatry*. 2012;73 Suppl 1:10-16.
- Charbonneau A, et al. Measuring the quality of depression care in a large integrated health system. *Med Care*. 2003;41(5):669-680.

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**CLINICAL RELEVANCE OF VILAZODONE TREATMENT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: CATEGORICAL IMPROVEMENT IN SYMPTOMS**

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**Background:** Vilazodone is a serotonin reuptake inhibitor and 5-HT<sub>1A</sub> receptor partial agonist approved by the FDA for the treatment of major depressive disorder (MDD) in adults. The Montgomery-Asberg Depression Rating Scale (MADRS) is a validated, clinician-rated scale used to measure MDD symptom severity and improvement following treatment; it comprises 10 items (Apparent Sadness, Reported Sadness, Inner Tension, Reduced Sleep, Reduced Appetite, Concentration Difficulties, Lassitude, Inability to Feel, Pessimism, Suicidal Thoughts). Each item score ranges from 0 to 6 with higher score indicating greater severity. The present analyses assessed clinically relevant symptom improvement in MADRS individual items by evaluating baseline to end of study (EOS) shifts from more to less severe symptom categories.

**Methods:** The analyses were conducted on pooled data from 2 positive, Phase III, 8-week, double-blind, randomized, placebo-controlled trials (NCT00285376 and NCT00683592) in outpatients (18 to 70 years) with DSM-IV-TR-defined MDD. Vilazodone dose was titrated over a 2-week period from 10 mg to a 40-mg target dose taken once daily with food. Post hoc analyses were conducted on study completers with 8 weeks of treatment. The shift analyses were done at 2 levels: patients with baseline score  $\geq 2$  (eg, sad but brightens without difficulty, slightly reduced sleep, occasional edginess) to an EOS score  $< 2$  ('minimal to no symptoms') and patients with baseline score  $\geq 4$  (eg, unhappy most of the time, sleep reduced by at least 2 hours, continuous tension/intermittent panic) to EOS score  $\leq 2$ . Odds ratios were estimated and Fisher's exact test was used to obtain the 2-sided nominal *P* values for comparisons between vilazodone and placebo.

**Results:** The percentage of patients with severity category shift from baseline  $\geq 2$  to EOS  $< 2$  was significantly higher for vilazodone vs placebo on all MADRS single items (OR range, 1.4 to 1.7;  $P \leq .05$ ) except Reduced Appetite (OR 1.3;  $P = .232$ ). In patients with greater symptom severity (baseline  $\geq 4$ ), more vilazodone than placebo patients shifted to  $\leq 2$  at EOS. Differences were statistically significant for vilazodone vs placebo on items of Apparent Sadness (60% vs 47%; OR, 1.7;  $P = .003$ ), Reported Sadness (60% vs 48%; OR, 1.6;  $P = .003$ ), Inner Tension (58% vs 41%; OR, 2.0;  $P = .003$ ), Reduced Sleep (51% vs 36%; OR, 1.8;  $P = .002$ ), and Lassitude (57% vs 47%; OR 1.5;  $P = .029$ ). For Item 10 (Suicidal Thoughts), OR was not evaluable.

**Conclusions:** Significantly greater proportion of patients treated with vilazodone compared with placebo achieved a shift from a baseline score  $\geq 2$  to EOS score  $< 2$  on all MADRS single items except Reduced Appetite. For patients with more severe symptoms (baseline score  $\geq 4$ ), significant improvements were noted on the items of Reported Sadness, Apparent Sadness, Inner Tension, Reduced Sleep, and Lassitude. Shifts to the 'minimal to no symptom' severity category demonstrated that vilazodone treatment is associated with clinically meaningful improvement in symptoms of MDD.

**Learning Objectives:**

- Evaluate the efficacy of vilazodone treatment in categorically improving the symptoms of depression in patients with major depressive disorder
- Compare the treatment effects of vilazodone in patients with different levels of symptom severity

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

**Literature References:**

- Khan A, Cutler AJ, Kajdasz DK, Gallipoli S, Athanasiou M, Robinson DS, Whalen H, Reed CR: A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. J Clin Psychiatry 2011; 72; 442-447.
- Rickels K, Athanasiou M, Robinson DS, Gibertini M, Whalen H, Reed CR: Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry; 2009; 70; 326-333.

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**A PROPOSAL TO IMPROVE THE DIAGNOSIS AND TREATMENT OF MAJOR DEPRESSION**

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**Specific purpose:** to improve diagnosis and treatment of major depression.

**Background:** Field trials of the DSM-V have revealed a kappa of 0.28 (in the questionable range) for the diagnosis of major depression. The DSM-V like DSM-IV requires 5 of 9 symptoms to diagnose a major depressive episode. Only 30% of treated depressed subjects attain remission, with another 30% receiving some benefit and 40% receiving no benefit at all. Current treatments of depression do not improve sexual function. In fact, the Serotonin Reuptake Inhibitors (SSRIs) and the Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) further compromise sexual function.

**Methods:** Major depression was diagnosed by DSM-IV criteria. Sexual function was measured by the Derogatis Inventory of Sexual Function with one standard deviation below normal selected as sexual dysfunction.

**Results:** In a review of 1791 subjects diagnoses with major depressive disorder, almost all subjects had 6 symptoms: depressed mood, loss of interest in activities, insomnia or hypersomnia, fatigue, worthlessness, and diminished ability to think. Three symptoms, however, were not universally agreed to: weight loss or gain 58%, psychomotor agitation 70%, and recurrent thoughts of death 40%. Sexual dysfunction, not one of the 9 diagnostic symptoms, was present in 82% of subjects.

**Conclusions:** We believe sexual dysfunction is an integral part of major depression and must be considered in the diagnosis and treatment of major depression. The problem has been that to date there have been no approved pharmacologic treatments or combinations of treatments that will improve both depression and sexual dysfunction. An improvement in the diagnosis and treatment of major depression would result from an a priori consideration and effective pharmacologic treatment of both depression and sexual dysfunction.

**Learning Objectives:**

- Improved diagnosis of major depression
- Treatment options after initial treatment failure

**Source of Funding:** Organon funded the clinical trials. Fabre Kramer analyzed the data and wrote the reports.

**Literature References:**

- R. Freedman et al.
- BN Gaynes et al.

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**AGREEING ON DEPRESSION SEVERITY: PATIENT VERSUS CLINICIAN RATINGS IN PRIMARY CARE**

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**Background:** Patient and clinician agreement on depression severity can form the basis for initial treatment decisions, and a foundation for future shared decision making.

**Objective:** To evaluate the agreement between patient and clinician ratings of depression severity in a secondary analysis of the Clinical Outcomes in MEasurement-based Treatment (COMET) trial.

**Methods:** Primary care physicians (n=83) recruited adult patients (n=908) diagnosed with major depressive disorder and newly prescribed antidepressant medication at study start. At baseline and 6 months, patients completed the Patient Health Questionnaire-9 item (PHQ-9), and patients and clinicians completed the global impression of severity (GIS). GIS severity scores were matched to published PHQ-9 severity benchmarks. Change from baseline GIS was analyzed by multivariate regression adjusted for patient demographic and clinical characteristics.

**Results:** At baseline (n=908), 56% of patient/clinician pairs agreed on GIS ratings, with 27% of clinician GIS scores higher than patient GIS scores, and 17% of patient GIS scores higher than the clinician GIS. Both patient and clinician GIS agreement with the PHQ-9 was 32%. GIS scores were lower than PHQ-9 for 58% of patient ratings and 54% of clinician ratings. At 6 months (n=578), 41% of patient/clinician pairs agreed on GIS ratings, 46% of clinician GIS scores were higher than patient GIS, and 13% of patient GIS scores were higher than clinician GIS. Patient-reported GIS was associated with a greater decrease in GIS from baseline to 6 months than clinician-reported GIS ( $p<0.001$ ). Agreement with the PHQ-9 was 55% for patient GIS and 39% for clinician GIS. GIS scores were lower than PHQ-9 for 32% of patient and 23% of clinician ratings.

**Conclusions:** At baseline a slight majority of patient and clinician ratings on the GIS were concordant. The tendency of clinicians to report higher severity in this population may stem from the enrollment criteria which required clinicians prescribe a new prescription for an antidepressant medication. At month 6, patients rated greater GIS improvement, which may represent a different reference point for clinicians (overall depressed population) vs patients (personal baseline). Discordance between PHQ-9 and GIS may partly reflect imperfect matching between PHQ-9 and GIS severity categories and GIS raters may have evaluated functioning as part of depression severity assessment. These results underscore the need for patient-physician collaboration and measurement-based care to make appropriate shared treatment decisions.

#### **Learning Objectives:**

- Measurement-based assessment
- Concordance between patient and clinician ratings

**Source of Funding:** Bristol-Myers Squibb, Otsuka Pharmaceutical Development & Commercialization, Inc

#### **Literature References:**

- Yeung AS, Jing Y, Brennen SK, et al. Clinical outcomes in measurement-based treatment (comet): a trial of depression monitoring and feedback to primary care physicians. *Depress. Anxiety*. 2012;29(10):865-873
- Tackling partial response to depression treatment. *Prim Care Companion J Clin Psychiatry* 2009; 11(4):155-62

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## **ANTIDEPRESSANTS: THE SPECTRUM BEYOND DEPRESSION FOR PEOPLE LIVING WITH HIV**

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**Introduction:** Despite HAART, people living with HIV (PLWH) still exhibit excessive morbidity risks, thus new adjuvant treatments are needed. Noteworthy, non-HIV studies suggest that antidepressants exert their beneficial effects by up-regulating BDNF and/or serotonin (5-HT), enhancing vascular function

(TGF-beta) or by anti-inflammatory actions. Since these postulates have not been validated in PLWH, but could represent an overlooked benefit, our goal was to explore antidepressants' clinical potential.

**Methods:** Analyses included 200 PLWH enrolled in the ongoing HIV/Tobacco cohort that completed the 6 month follow-up visits. All subjects completed standardized research surveys, including the Beck Depression Inventory II (BDI). Using state of the art technology the CD4 count, viral load, concentrations of 5-HT, BDNF, and a set of inflammatory and vascular markers (IL-4, IL-6, IFN, TNF, IL-10, IL-12, and TGF-beta) were measured, to determine any changes in these levels if subjects reported having used an approved pharmacological treatment for depression.

**Results:** At baseline 42% of the group suffered depression (BDI=19-63), and only half were receiving antidepressants (54%), resulting in three well-balanced groups for analyses. Notably, depressed PLWH exhibited 5-HT ( $91 \pm 11$  vs.  $88 \pm 5$  ng/ml,  $p=0.8$ ) and BDNF levels ( $8474 \pm 6365$  vs.  $8485 \pm 6439$  pg/ml,  $p=0.9$ ) that were quite similar to those of the non-depressed ones. Compared with those without depression, depressed subjects were characterized for higher levels of IL-6 ( $5.9 \pm 1.8$  vs.  $4.3 \pm 0.3$  pg/ml,  $p=0.05$ ) and TGF-beta1 ( $543 \pm 2$  vs.  $4.3 \pm 0.3$  pg/ml,  $p=0.05$ ). On the other hand, antidepressants were associated with reduced levels of TNF-alpha ( $2 \pm 0.2$  vs.  $2.7 \pm 0.2$  pg/ml,  $p=0.05$ ), INF-gamma ( $2915 \pm 364$  vs.  $1963 \pm 295$  pg/ml,  $p=0.04$ ), IL-6 ( $4.2 \pm 0.3$  vs.  $5.6 \pm 1.3$  pg/ml,  $p=0.3$ ) and TGF-beta ( $494 \pm 46$  vs.  $364 \pm 28$  pg/ml,  $p=0.3$ ), suggesting that an increase in TGF-beta may be state-related. Longitudinal analyses revealed improvements on BDI scores ( $-17.5 \pm 1.7$ ,  $p=0.001$ ), and increases on 5-HT ( $+9.8 \pm 1.4$  ng/ml,  $p=0.5$ ) among those receiving antidepressants. On the other hand, depressed subjects without antidepressants, while improved somehow their BDI scores ( $-16.3 \pm 1.7$ ,  $p=0.000$ ), exhibited a decline in 5-HT ( $-1.5 \pm 0.2$  ng/ml,  $p=0.9$ ). Similarly, PLWH without depression, BDI score decreased ( $-3.4 \pm 0.9$ ,  $p=0.000$ ), and 5-HT levels dropped ( $-16.8 \pm 12$  ng/ml,  $p=0.2$ ).

**Conclusions:** While global improvements on BDI scores were observed, findings argue against the notion that improvements on depression are associated with normalization of serotonin or BDNF levels. Nevertheless, data provide first evidence that among PLWH, antidepressants might decrease chronic inflammation. This unrecognized benefit underscores the importance of providing antidepressants to PLWH battling with depression, and highlights the need of additional studies in this area.

#### **Learning Objectives:**

- To assess the different theories of depression on PLWH
- To explore novel therapeutic benefits based on these theories

**Source of Funding:** 1. Florida Health Department James & Esther King K10 Title: Cytokines: an Underlying Cause of Health Disparities in Tobacco Related Diseases  
2. NIAAA R01 AA018095-01A1 Title: Platelets Mediating Alcohol and HIV Damage

#### **Literature References:**

- Jaegyu H, et al. Inhibition of glial inflammatory activation and neurotoxicity by tricyclic antidepressants. *Neuropharm.* 2008; 55: 826-834.
- Maes, M. Editorial: (Neuro)inflammation and neuroprogression as new pathways and drug targets in depression: from antioxidants to kinase inhibitors. *Progress in Neuro-Psychopharm & Biol Psychiatry.* 2011; 35: 659-663.

#### **SAFETY AND TOLERABILITY OF LEVOMILNACIPRAN SR IN MAJOR DEPRESSIVE DISORDER: RESULTS FROM AN OPEN-LABEL, 48-WEEK EXTENSION STUDY**

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**Objective:** Levomilnacipran (1S, 2R-milnacipran), is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with approximately 2-fold greater potency for reuptake inhibition of norepinephrine relative to serotonin. Levomilnacipran SR is in late-stage clinical development for the treatment of major depressive disorder (MDD) in adults; a sustained release (SR) formulation was developed for once-daily dosing. This open-label extension study evaluated the long-term safety and

tolerability of levomilnacipran SR in patients who completed 1 of 3 Phase III fixed- (NCT00969709) or flexible-dose (NCT00969150, NCT01034462) lead-in studies.

**Methods:** Patients who completed 1 of the lead-in studies were eligible to participate in this open-label extension study (NCT01034267) to evaluate the long-term safety and tolerability of levomilnacipran SR 40-120 mg/d. This study comprised a 48-week, open-label treatment period followed by a 4-week down-taper period. Safety assessments included adverse events (AEs), laboratory tests, vital signs, ECGs, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Analyses were based on the Safety Population (all patients who received  $\geq 1$  dose of open-label levomilnacipran); baseline for all safety analyses was the respective lead-in study baseline.

**Results:** The Safety Population comprised 825 patients who entered the extension study; 47% completed the study. The mean (median) duration of treatment was 222 (280) days; mean dose was 82.7 mg/d. Serious AEs were reported in 36 (4%) patients; 7 were considered related to levomilnacipran SR treatment. Discontinuations due to AEs occurred in 13% of patients; most frequent were nausea (1%) and hyperhidrosis (1%). Treatment-emergent AEs (TEAEs) were reported in 86% of patients; most TEAEs were mild to moderate in severity. The most common TEAEs ( $\geq 10\%$ ) were headache (22%), nausea (16%), upper respiratory tract infection (13%), hyperhidrosis (11%), and constipation (10%). During the down-taper period, 9% of patients had a newly emergent TEAE. Mean changes from baseline in laboratory parameters were small and not clinically meaningful. Mean increases from baseline in pulse rate (9 bpm), and systolic (4 mmHg) and diastolic BP (3 mmHg) were seen. Potentially clinically significant (PCS) increase in diastolic BP ( $\geq 105$  mmHg and increase  $\geq 15$  mmHg from baseline) occurred in 2% of patients; the incidence of PCS changes in other vital signs was  $<1\%$ . Mean changes from baseline in ventricular heart rate, QTcB, and QTcF interval were 13 bpm, 11 msec, and -1 msec, respectively; PCS ECG values occurred in  $<1\%$  of patients. The occurrence of C-SSRS-rated suicidal ideation was reported in 22% of patients (primarily in the least severe category, "wish to be dead," in 13% of patients); suicidal behavior was reported in  $<1\%$  patients.

**Conclusions:** Levomilnacipran SR 40-120 mg/day administered for up to 1 year was generally safe and well tolerated. TEAEs were consistent with the AE profile of other SNRIs.

#### **Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the long-term safety profile of levomilnacipran SR in patients with MDD.
- At the conclusion of this session, the participant should be able to discuss the adverse event profile of levomilnacipran SR in long-term use.

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

#### **Literature References:**

- Greenberg WM, Gommoll C, Bose A, Li H, Ruth A: P.2.c.021. Levomilnacipran in the treatment of major depressive disorder: an analysis of efficacy and safety data from two phase III studies. *Eur Neuropsychopharmacol.* 2012;22(suppl 2):S262.
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### **PH 10 MAY BE A NEW RAPIDLY ACTING INTRANASALLY ADMINISTERED ANTIDEPRESSANT**

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**Purpose:** There is a well-recognized need for more rapidly acting antidepressants. A novel class of compounds called pherines, which are intranasally administered neurosteroids, may have rapid and potent effects on major psychiatric syndromes. Positive placebo controlled results from PH94B in social anxiety



disorder were presented at NCDEU in 2011. Here we present preliminary promising placebo controlled trial data on PH 10 in patients with major depression (MDD).

**Introduction:** PH 10 is a pherine, a small molecule that specifically engages peripheral chemoreceptors in the nasal passages, and triggers neural impulses that modulate the function of the limbic system, amygdale, hypothalamus, anterior cingulate gyrus and frontal cortex. After demonstrating safety in animals and normal human volunteers, a placebo controlled trial of PH 10 was initiated in patients with MDD.

**Methodology:** Thirty patients with MDD and a HAM-D -17 score of  $\geq 17$  were randomized to receive intranasally low dose PH10 (3200 ng/day), high dose PH10 (6400 ng/day) or placebo for 8 weeks. The primary outcome measure was the endpoint HAM-D score. Secondary outcome measures included changes in HAM-D scores during the 8 weeks of treatment, and CGI, and Q-LES-Q-SF.

**Results:** Results of the ANCOVA for group differences in HAMD scores (baseline HAMD as covariate) indicated a trend toward adjusted group differences at endpoint ( $F(2,26) = 2.95$ ,  $p = 0.070$ ). Exploratory pairwise comparisons for the least squares-adjusted group means indicated a trend toward difference between the placebo (mean = 10.36) and high dose group (mean = 6.15) at  $t(18) = 2.23$ ,  $p = 0.085$ . The low dose adjusted mean (6.60) was not statistically different from that of other groups.

Further exploration showed an effect size (Cohen's d) of 1.13 for the low dose group and 0.77 for the high dose group when compared to the placebo group at endpoint. Rapid antidepressant benefit was also seen, with the low dose group showing an effect size of 1.05 and the high dose group 0.75 in comparison to placebo after one week of treatment.

Response ( $\geq 50\%$  improvement on HamD) and remission (HamD  $\leq 7$ ) rates at endpoint were, respectively, 80% and 60% for low dose, 90% and 80% for high dose, and 60% and 20% for placebo. High-dose exceeded placebo in remission rate, ( $z = 3.35$ ,  $p = 0.023$ ), with low dose and placebo not statistically different ( $z = 2.00$ ,  $p = 0.170$ ) and no difference between the high and low dose ( $z = 1.00$ ,  $p = 0.628$ ).

Group response rates were not statistically different. Comparisons on GGI and QLES Q at endpoint were not significant.

Side effects included increased appetite, day time sleepiness, nasal dryness and headache. Weight gain did not differ among groups.

**Discussion:** These very preliminary results suggest Ph10 may be a novel, rapidly acting, potent and well tolerated antidepressant. Further trials are clearly indicated.

#### **Learning Objectives:**

- 1. To familiarize attendees with the antidepressant efficacy of PH10
- 2. To explore the rapidity of onset of antidepressant effects of PH10

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### **THE SELECTIVE METABOTROPIC GLUTAMATE 2/3 RECEPTOR ANTAGONIST (BCI-632) IN DEVELOPMENT FOR TREATMENT RESISTANT DEPRESSION: PHASE 1 SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS**

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Treatment resistant depression (TRD) is defined as the failure to fully respond to an antidepressant treatment despite having had an adequate dose and duration of treatment<sup>1</sup>. The need for medication that effectively and safely treat TRD is unmet. Research in depression has been strongly influenced by the finding that a single administration of a sub-anesthetic dose of ketamine leads to rapid and long lasting efficacy in patients with TRD. The mechanism by which ketamine confers this activity involves a rapid increase in synaptic glutamate, AMPA receptor activation, increased BDNF translation and activation of mTOR leading to increased synthesis of synaptic proteins<sup>2,3</sup>. The same signaling cascade is triggered by selective antagonists of the metabotropic glutamate receptor (mGlu) 2/3, such as LY341495 or BCI-632<sup>4</sup>. We report Phase 1 data for BCI-838, the oral prodrug of BCI-632, dosed to healthy male and female

subjects in a single ascending dose (SAD) and a multiple ascending dose (MAD) study. Safety and tolerability were monitored and plasma was collected for pharmacokinetic (PK) analysis. In the MAD study, electroencephalograms (EEGs) were collected to assess pharmacodynamic (PD) effects on the central nervous system. In the SAD study (n=25), single doses of BCI-838 up to 900 mg were given under fasted conditions. BCI-838 was well tolerated. PK analysis showed dose-dependent increases in BCI-632 and BCI-838 plasma levels that were slightly less than dose-proportional. A food effect sub-study included showed an increase in BCI-632 plasma levels when BCI-838 was dosed with food. In the MAD study (n=30), BCI-838 was given under fed conditions for 7 days at doses up to 600 mg QD. At 100 and 300 mg, BCI-838 was well tolerated. At 600 mg, a dose well above the estimated therapeutic range, an increase in AEs of mild to moderate severity was noted. PD analysis of the qEEG data showed dose-dependent effects on the EEG signal indicating brain penetration. The compelling clinical data obtained for BCI-838 support the drug's advancement into a proof-of-concept study in patients with TRD.

#### **Learning Objectives:**

- Become familiar with the mechanism of action of BCI-632, an mGluR2/3 antagonist in development for TRD.
- Review the Phase 1 safety, PK and PD data for BCI-632 and its prodrug, BCI-838.

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

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### **LISDEXAMFETAMINE DIMESYLATE AUGMENTATION EFFECTS ON EXECUTIVE FUNCTION IN MAJOR DEPRESSIVE DISORDER: IMPACT OF BASELINE SSRI MONOTHERAPY**

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**Purpose:** The precise nature of cognitive dysfunction in depression and the cognitive effects of selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder (MDD) is not well understood. In a multicenter, double-blind, placebo (PBO)–controlled trial in adults with MDD, lisdexamfetamine dimesylate (LDX) augmentation of SSRI monotherapy significantly improved executive function versus PBO as measured by the self-reported Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A). To understand how concomitant SSRI monotherapy and LDX augmentation may impact executive function, post hoc analyses were conducted to examine BRIEF-A changes stratified by baseline SSRI monotherapy.

**Methods:** Adults (18–55 y) with Montgomery-Asberg Depression Rating Scale total score ≤18 and BRIEF-A Global Executive Composite (GEC) T score ≥60 who received ≥8 weeks of SSRI monotherapy were screened for 2 weeks and then randomized to 9 weeks of double-blind LDX (wk 1, 20 mg/d; wks 2–

6, titrate in 10-mg weekly increments [maximum, 70 mg/d]; wks 7–9, maintain optimized dosage) or PBO augmentation followed by 2 weeks of single-blind PBO. The primary endpoint, BRIEF-A Self-Report GEC T score change from baseline to week 9/end of study (EOS), was assessed using ANCOVA with last observation carried forward in randomized participants who took  $\geq 1$  study drug dose and had  $\geq 1$  postbaseline BRIEF-A assessment. Post hoc analyses descriptively present mean BRIEF-A GEC T score changes at week 9/EOS stratified by baseline SSRI monotherapy; the study was not powered for comparative analysis of these data. Treatment-emergent adverse events (TEAEs) are also presented.

**Results:** Mean  $\pm$  SD BRIEF-A GEC T score changes at week 9/EOS were  $-12.8 \pm 13.89$  with PBO ( $n=72$ ) and  $-21.6 \pm 14.55$  with LDX ( $n=71$ ); the least squares mean (95% CI) treatment difference favored LDX ( $-8.0 [-12.7, -3.3]$ ;  $P=0.0009$ ). Mean  $\pm$  SD BRIEF-A GEC T score changes for PBO vs LDX, respectively, varied by baseline SSRI: citalopram ( $-10.7 \pm 16.45$  [ $n=20$ ] vs  $-27.3 \pm 13.15$  [ $n=19$ ]), escitalopram ( $-11.7 \pm 13.54$  [ $n=22$ ] vs  $-22.3 \pm 13.86$  [ $n=11$ ]), sertraline ( $-12.6 \pm 10.10$  [ $n=12$ ] vs  $-18.3 \pm 13.47$  [ $n=12$ ]), fluoxetine ( $-14.8 \pm 13.34$  [ $n=16$ ] vs  $-14.4 \pm 13.73$  [ $n=18$ ]), paroxetine ( $-22.0 \pm 16.78$  [ $n=5$ ] vs  $-21.5 \pm 16.51$  [ $n=16$ ]). The frequency of TEAEs during augmentation was 73.6% (53/72) with PBO and 78.9% (56/71) with LDX.

**Conclusion:** In this exploratory, post hoc analysis, LDX augmentation of citalopram or escitalopram monotherapy produced the largest numerical effects on executive functioning relative to other baseline SSRIs. Additional studies are needed to confirm these findings.

#### **Learning Objectives:**

- Understand the persistent nature of cognitive impairment in MDD
- Describe the LDX augmentation effects on executive function in individuals with MDD

**Source of Funding:** Shire Development LLC

#### **Literature References:**

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#### **SUSTAINED IMPROVEMENT IN FUNCTIONAL HEALTH AND WELL-BEING IN MDD PATIENTS FOLLOWING LONG-TERM TREATMENT WITH LEVOMILNACIPRAN SR**

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**Objectives:** Levomilnacipran (1S, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with approximately 2-fold greater potency for reuptake inhibition of norepinephrine than serotonin. A sustained release (SR) formulation was developed for once-daily dosing. Levomilnacipran SR is in late-stage clinical development for major depressive disorder (MDD). Analyses were conducted to evaluate the long-term benefits of levomilnacipran SR treatment on the functional health and well-being of adult MDD patients as measured by the SF-36v2 Health Survey.

**Methods:** Patients with MDD who completed 1 of 3 placebo-controlled studies (lead-in studies) were eligible to participate in this open-label extension study (NCT01034267), consisting of a 48-week open-label treatment period with levomilnacipran SR 40-120 mg/d. During the study, the SF-36v2 acute version was administered every 12 weeks. The mean change from baseline (start of lead-in study) to Week 48 for each of the eight individual health domains: [Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), Mental Health (MH)], and the Physical (PCS) and Mental (MCS) Component Summary scores were analyzed using Observed Cases with Last Observation Carry Forward (LOCF) used as a sensitivity

analysis. The SF-36 utilizes norm based scoring, with a mean of 50 and a standard deviation (SD) of 10 based on the U.S. general population. Higher scores and positive change represent improvement. For group-level data, mean scores that are within 0.3 SD (47-53) are considered to be in the “average” or “normal” range.

**Results:** A total of 811 patients in the intent-to-treat population had a baseline SF-36 evaluation. Mean baseline scores (SD) indicated significant deficits ( $>1.0$  SD) for the domains of MH 24.53 (8.05), RE 24.58 (10.25), SF 26.72 (9.35), VT 30.89 (7.14) and the MCS 18.97 (9.22). Baseline scores for RP 40.40 (12.50), GH 41.89 (9.77), BP 42.96 (10.45) and PF 45.69 (10.79) were within 1.0 SD, but still below the “normal” threshold (47). Mean baseline PCS score 50.60 (10.91) was within the normal range. In the mean change from baseline analysis, 378 patients completed 48-weeks of treatment in the extension study. Improvements from baseline were noted for all individual health domains, which were maintained over the study period. Greatest improvement was seen in MH 22.19 (13.62), followed by RE 20.87 (14.32), SF 20.24 (13.52), VT 18.51 (12.76), RP 8.45 (13.01), GH 8.01 (9.49), BP 7.01 (11.57) and PF 5.48 (10.53). Significant improvement was noted for the MCS 26.53 (15.42), with minimal change for PCS 0.99 (10.22). At end of treatment, all scores were within 1.0 SD of the population norm, and all domains except for RE reached the normal range. Similar trends were observed using LOCF.

**Conclusions:** Long-term treatment with levomilnacipran SR in patients with MDD resulted in sustained improvement in functional health and well-being as measured by the SF-36. Improvement was observed in all eight of the individual health domains and the MCS and PCS summary scores.

**Learning Objectives:**

- Learn about the baseline profile of MDD patients based on the SF-36 Health Survey.
- Learn about the long term benefits of levomilnacipran SR treatment on functional health and well-being based on improvement in the SF-36 health domains and component summary scores.

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

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**POPULATION PHARMACOKINETIC MODELING TO ASSESS THE IMPACT OF BASELINE COVARIATES ON LEVOMILNACIPRAN EXPOSURES IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER**

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**Objectives:** To evaluate the potential effects of demographic characteristics, renal function, and liver function on steady-state exposures of levomilnacipran and to provide a model-based recommendation for dose adjustment in patients with major depressive disorder.

**Methods:** The population pharmacokinetic (PK) analysis used levomilnacipran plasma concentration data from a pooled dataset of 13 Phase I (458 subjects with rich sampling) and 3 Phase III studies (798 subjects with sparse sampling). Daily dose in the pooled dataset ranged from 20 to 300 mg. Standard pharmacometric techniques for model building, covariate selection, and goodness-of-fit were used to select the final model. An exploratory assessment of the effect of concomitant medication on the steady-state exposure to levomilnacipran was conducted for the Phase III subjects.

**Results:** A one compartment pharmacokinetic model with delayed first order absorption and first order elimination best described the pharmacokinetics of levomilnacipran. Plasma concentrations increased proportionally to dose over the therapeutic range. The primary clinical covariate influencing exposure to levomilnacipran was renal function. For subjects with mild, moderate and severe renal impairment, the final model showed reductions in median clearance of 20%, 40%, and 58%, respectively, compared with a typical subject with normal renal function. Simulations of the final model identified dose adjustment strategies for varying degrees of renal impairment, including mild (CLCR 60 - 89 [mL/min]), moderate (30 - 59) and severe (15 - 29). Concomitant medications did not show an impact on levomilnacipran exposures in this dataset, but fewer than 3% of the Phase III subjects were taking the concomitant medications investigated for a possible impact on exposures.

**Conclusions:** Renal function was the only covariate found to be clinically relevant. While no dose adjustment is needed for subjects with mild renal impairment, the maintenance dose for subjects with moderate and severe renal impairment should not exceed 80 mg and 60 mg once daily, respectively, in comparison to the maximum therapeutic dose of 120 mg daily for subjects with normal renal function. In addition, adjusted dose titration schedules are recommended for subjects with moderate and severe renal impairment to achieve levomilnacipran exposures similar to those in subjects with normal renal function.

**Learning Objectives:**

- To understand the population pharmacokinetics of levomilnacipran
- To understand the pharmacokinetic basis for dosage adjustments of levomilnacipran according to renal function category

**Source of Funding:** All studies referenced in this abstract were funded by Forest Laboratories, Inc.

**Literature References:**

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**SPEAKING A MORE CONSISTENT LANGUAGE WHEN DISCUSSING SEVERE DEPRESSION: A CALIBRATION STUDY OF THREE SELF-REPORT MEASURES OF DEPRESSIVE SYMPTOMS**

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**Objective:** We recently found marked disparities between three self-report scales that assess the DSM-IV criteria for major depression in the percentage of depressed outpatients considered to have severe depression. The goal of the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) was to calibrate the measures against a clinician-rated “gold standard”, and to establish a cutoff point on each of the scales that identifies a similar prevalence of severe depression and increases the level of agreement between the scales in identifying severe depression.

**Methods:** Three hundred fifty-three depressed outpatients completed the Clinically Useful Depression Outcome Scale (CUDOS), Quick Inventory of Depressive Symptomatology (QIDS), and Patient Health Questionnaire (PHQ-9). The patients were also rated on the 17-item Hamilton Depression Rating Scale (HAMD).

**Results:** Based on the scale developers’ recommended cutoffs for severe depression, the level of agreement between the pairs of scales was low (mean overall level of agreement 64.4%,  $k = .30$ ). After calibration, the self-report scales identified a similar percentage of patients as severely depressed (range 22.2% to 26.5%), and the level of agreement between the scales in identifying severe depression increased (mean overall level of agreement 81.4%,  $k = .48$ ).

**Discussion:** If clinicians are to follow treatment guidelines' recommendations to base initial treatment selection on the severity of depression, then it is important to have a consistent method of determining depression severity. The present calibration study of three self-report depression questionnaires identified cutoff scores that resulted in similar prevalence rates of severe depression and increased the level of agreement between the scales. Calibration studies of this type will be increasingly important when different scales are used to measure the same construct, and the construct being measured has clinical importance such as determining treatment approaches.

**Learning Objectives:**

- The participant will become aware that there is a marked disparity between standardized scales in the classification of depressed outpatients into severity groups.
- The participant will become aware of new, empirically derived cutoff scores from a calibration study that resulted in similar prevalence rates of severe depression and increased the level of agreement between the scales

**Source of Funding:** Eli Lilly

**Literature References:**

- 206. Zimmerman, M., Martinez, J., Friedman, M., Attiullah, N., Boerescu, D.A. & Toba, C. How Can We Use Depression Severity to Guide Treatment Selection When Measures of Depression Categorize Patients Differently? *Journal of Clinical Psychiatry*, in press
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**MEDICARE PATIENT EXPERIENCE WITH VAGUS NERVE STIMULATION FOR TREATMENT-RESISTANT DEPRESSION**

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**Background:** Major depressive disease (MDD) represents a cost burden to the US healthcare system: about one-third of MDD patients fail conventional treatment. Multiple failures define treatment-resistant depression (TRD). Vagus nerve stimulation (VNS) therapy is an approved adjunctive treatment for TRD. We studied the healthcare utilization experience of Medicare beneficiaries implanted with VNS (VNSBs) during Medicare coverage compared with beneficiaries with TRD (TRDBs) and managed depression (Mdeps).

**Methodology:** A retrospective analysis of 100% standard analytic file (SAF) Medicare claims from 2006-2009 using specific criteria to identify a VNSB dataset was compared to TRDs and Mdeps datasets (extract of 5% sample SAF from 2001-2009) and 2009 general Medicare beneficiaries (GMBs). Comparative analysis included demographics, mortality, healthcare utilization, and costs.

**Results:** Of patients meeting study criteria for VNSBs (n=690), TRDBs (n=4,639), Mdeps (n=7,524) and GMBs (n>36 million), VNSBs were on average: younger, more likely to be female, and white, with Medicare eligibility due to disability. Of the VNSBs in the 2-year post-implant period: 5% died, 22% experienced no negative events (defined as hospitalizations for psychoses or poisoning, emergency room use, electroconvulsive therapy, or poisoning, suicidal ideation, or self-harm diagnoses); 29% experienced multiple negative events; and 41% had either a single hospitalization or only all-cause ER visits. VNSBs experiencing negative events had more complex co-occurring psychiatric diagnoses. The annual mortality rate for VNSBs post-implant was 19.9 deaths per 1000 patient years, compared with 46.2 (CI: 41.9-51.6) and 46.8 (CI: 43.4-50.4) deaths for TRDBs and Mdeps, respectively. The medical costs per patient-year post-VNS implantation for VNSBs (\$8749) was similar to the Medeps (\$8960; CI \$8555-\$9381) and was substantially lower than TRDBs (\$13618; CI \$12937-\$14342).

**Conclusion:** VNSBs achieving positive health outcomes (measured by lack of negative events post-implantation) tend to have fewer psychiatric co-occurring conditions than TRDBs who were not implanted with VNS. Post-implantation costs lower than those for TRDBs with evidence of response to

VNS suggest the therapy represents an option for carefully screened TRDBs who have failed other therapies.

**Learning Objectives:**

- Participants will learn the characteristics for Medicare VNS, matched TRD, and managed depression populations
- Participants will become familiar with the impact of VNS on positive health outcomes and patient selection criteria

**Source of Funding:**

Cyberonics, Inc., sponsored the study through a contract with The Moran Company. Independence in the methods, analyses, and interpretation of the results was a condition of the contract with The Moran Company.

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**IS ESCITALOPRAM A BETTER ANTIDEPRESSANT THAN BUPROPION?**

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**Introduction:** STAR\*D reported only about a third of patients with major depressive disorder remit with first or second monotherapy, including with SSRI or bupropion. Demonstrations of increased remissions and/or superiority of one antidepressant over another are rare. We report a post hoc analysis of escitalopram relative to bupropion.

**Method:** Two hundred forty-five adult outpatients with major depression were randomly assigned to 12 weeks' treatment with bupropion (to 450 mg/d), escitalopram (to 40 mg/d) or the combination at the same doses, obtaining baseline and post treatment 17- and 29-item Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptoms, 16-item Self-Report Version, (QIDS-SR-16). The prospective study hypotheses compared combination therapy separately to each monotherapy, demonstrating some advantages relative to bupropion but only an advantage at week 2 relative to escitalopram. This report focuses on the two monotherapies in post hoc analyses.

**Results:** Seventy-eight patients were assigned combination treatment, 83 bupropion monotherapy and 84 escitalopram monotherapy. Escitalopram mean dose was  $26 \pm 13$  mg/d for combination patients and  $30 \pm 13$  mg/d in the escitalopram monotherapy group (NS), and bupropion's mean dose was  $324 \pm 141$  mg/d for patients receiving combination therapy and  $322 \pm 137$  for bupropion monotherapy patients (NS). On all ratings, covarying for baseline scores, escitalopram was superior to bupropion. Remission rates also differed between monotherapies. For example, by the HAMD-17, 52% (44/84) remitted with escitalopram vs. 34% (28/83) with bupropion ( $\chi^2 = 4.39$ ,  $df = 1$ ,  $p < .04$ ).

**Discussion:** This study was not designed to compare monotherapies, so these findings were unexpected and post hoc. Therefore, they must be taken as hypothesis generating rather than as 'proven'. If not fortuitous, it is surprising, as monotherapies for depressive disorders have rarely differed in efficacy. Level 2 of STAR\*D, for example, did not show differences among monotherapies, including between an SSRI (sertraline) and bupropion, whose dosing and remission rates were similar to those in the current study. A difference in the current study is maximal dose of escitalopram was twice that recommended in the PDR while bupropion dose was limited to that recommended by the PDR. The "superdosed" escitalopram demonstrated a higher remission than both bupropion and STAR\*D's SSRI which was dosed according to PDR recommendations. Further studies might address whether PDR dosing recommendations maximize remissions.

**Learning Objectives:**

- More than 1/3 of depressed patients can benefit from initial antidepressant medication.
- High dose escitalopram is better as initial treatment for major depression than maximal marketed dose of bupropion.

**Source of Funding:** NIMH grants R01MH076961 and R01MH077285; study medication was supplied by Forest Laboratories, Biovail Corporation and Lundbeck Canada.

**Literature References:**

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**A PATIENT-LEVEL META-ANALYSIS OF STUDIES EVALUATING VAGUS NERVE STIMULATION THERAPY FOR TREATMENT-RESISTANT DEPRESSION**

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**Background:** This study compared response and remission rates in depressed patients with chronic treatment-resistant depression (TRD) treated with vagus nerve stimulation (VNS) Therapy® plus treatment as usual (VNS+TAU) or TAU alone.

**Methodology:** We used data from 6 outpatient, multicenter clinical trials which evaluated VNS+TAU or TAU in TRD. These included 2 single arm studies of VNS+TAU, a single arm study of TAU, a nonrandomized registry of VNS+TAU and TAU, a randomized trial of different intensities of VNS, and a 12-week randomized trial of VNS+ TAU. This meta-analysis is based on individual level patient data and includes all patients with >1 post-baseline visit. Response and remission were based on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions scale's Improvement subscale (CGI-I). Treatments were compared using Bayesian hierarchical models appropriate for repeated measures data and that included a propensity score for each patient.

**Results:** Outcomes were compared from baseline up to 96 weeks of treatment between VNS+TAU (n=1,035) and TAU (n=425). The model-based MADRS response rates for VNS+TAU at 12, 24, 48, and 96 weeks were 12%, 18%, 28%, and 32% versus 4%, 7%, 12%, and 14% for TAU. The MADRS remission rate for VNS+TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14% versus 1%, 1%, 2%, and 4% for TAU. Adjunctive VNS Therapy was associated with a greater likelihood of MADRS response (odds ratio [OR] = 3.19, 95% confidence interval [CI]: 2.12, 4.66) and MADRS remission (OR=4.99, CI: 2.93, 7.76), compared with TAU. For patients who had a MADRS response to VNS+TAU at 24 weeks, sustained MADRS response was more likely at 48 weeks (OR=1.98, CI: 1.34, 3.01) and at 96 weeks (OR=3.42, CI: 1.78, 7.31). Similar results were observed for CGI-I response.

**Conclusion:** For chronic TRD patients, VNS+TAU has greater MADRS and CGI-I response and MADRS remission rates that are more likely to persist than TAU.

**Learning Objectives:**

- Participants will learn the general characteristics of VNS and TAU study populations.
- Understand use of laboratory paradigms to test preliminary pharmacotherapy efficacy

**Source of Funding:**

Cyberonics, Inc., sponsored the studies included in this meta-analysis, and commissioned Dr. Berry and Ms. Broglio of Berry Consultants to perform independent statistical analyses.

**Literature References:**



- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *Am J Psychiatry* 2006; 163:1905-1917
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## A SINGLE-DOSE PHARMACOKINETIC STUDY OF LEVOMILNACIPRAN SR IN SUBJECTS WITH NORMAL OR IMPAIRED RENAL FUNCTION

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**Objective:** Levomilnacipran (1S, 2R-milnacipran), is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI). Levomilnacipran is in late-stage clinical development for the treatment of major depressive disorder in adults; a sustained release (SR) formulation was developed for once-daily dosing. Renal excretion is a major route of elimination of levomilnacipran SR from the body. This study evaluated the pharmacokinetic (PK) and safety profile of levomilnacipran SR in subjects with impaired renal function compared with subjects with normal renal function.

**Methods:** A single-dose, open-label, parallel-group study of 32 male and female subjects (age 18-80 years). Subjects were categorized into 4 groups (8 subjects each), according to creatinine clearance (CL<sub>cr</sub>) value using the Cockcroft-Gault equation: normal renal function  $\geq 80$  mL/min; mild impairment  $\geq 50$  and  $< 80$  mL/min; moderate impairment  $\geq 30$  and  $< 50$  mL/min; severe impairment  $> 5$  and  $< 30$  mL/min. Healthy subjects with normal renal function were age-, weight-, and gender-matched to subjects with renal impairment. All subjects received a single oral dose of levomilnacipran SR 40 mg with 240 mL of water on Day 1 under fasted conditions. PK samples of blood (predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96 hours postdose) and urine (predose, 0-4, 4-8, 8-12, 12-16, 16-32, 32-48, 48-72, 72-96 hours postdose) were collected and assayed using validated liquid chromatography-mass spectrometry methods. Descriptive statistics were provided by group for PK parameters; log-transformed C<sub>max</sub> and AUC were compared between normal and renally impaired groups using a mixed-effects model with group as a fixed effect. Safety assessments included adverse events (AEs), laboratory evaluations, vital sign assessments, C-SSRS, and ECGs.

**Results:** All subjects completed the study. Following a single dose of levomilnacipran SR 40 mg, mean (SD) values for C<sub>max</sub> [ng/mL] in subjects with normal renal function, and mild, moderate or severe renal impairment were 83.9 (21.0), 81.8 (23.4), 98.7 (18.1), 122.1 (35.1) respectively; for AUC<sub>0-∞</sub> [h•ng/mL] values were 2101.0 (516.9), 2587.8 (649.9), 4016.4 (995.4), 5900.8 (1799.3); for T<sub>1/2</sub> [h], values were 13.5 (2.8), 17.3 (3.5), 19.1 (4.6), 27.7 (7.4), respectively. Renal clearance was 175.9 mL/min in normal subjects and 114.7, 69.9, and 28.6 mL/min in subjects with mild, moderate, and severe renal impairment, respectively. Levomilnacipran SR was generally well tolerated across groups. There were no serious AEs and no notable changes in mean laboratory values or vital signs except for mean increases in pulse rate in all groups (range: +6.6 to +10.9 bpm) and increased mean postdose systolic BP in the severe renal impairment group (+3.0 mm Hg). Based on simulations using a population PK model, reduced doses for subjects with moderate or severe renal impairment according to FDA 2010 guidance are recommended.

**Conclusions:** Renal impairment is associated with increased levomilnacipran exposure and prolonged T<sub>1/2</sub>; recommended maximum maintenance doses of levomilnacipran SR for patients with moderate and severe renal impairment should not exceed 80 mg and 60 mg daily, respectively.

**Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the pharmacokinetics of levomilnacipran SR in patients with renal impairment.
- At the conclusion of this session, the participant should be aware of the recommendation for adjusted dosing of levomilnacipran SR in patients with moderate and severe renal impairment.

#### **Source of Funding:**

This study was funded by Forest Laboratories, Inc.

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### **THE CONTRIBUTION OF BIOMARKERS TO CHANGES IN COGNITIVE MEASUREMENT IN ALZHEIMER'S DISEASE**

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**Background:** Alzheimer's disease (AD) is a major public health concern given aging populations worldwide. Efforts to better understand AD have included epidemiologic studies and clinical trials, some of which have used different biomarkers for AD. These different biomarkers could be used to elucidate further the causal pathways that contribute to cognitive domains in AD. This study investigates the association of cognitive domains of the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and the Mini-Mental State Examination (MMSE) with biomarkers of AD pathophysiology (specifically the presence of the *Apolipoprotein E (APOE)* in patients diagnosed with AD.

**Methods:** AD data was obtained from the Critical Path Institute Online Data Repository (CODR). We studied 1,158 patients with AD (507 APOE non-carriers, 146 Homozygous, 505 APOE carriers) who had cognition data available. Cognition variables included change in scores from Week 1 to Week 4 on each item of the ADAS-Cog, ADAS-Cog Total Score and the MMSE total score. We applied 2 independent methods-partial correlation analysis adjusted for age and gender and path analysis to evaluate the associations between biomarkers and cognition. Comparative Fit Index (CFI) and Normed Fit Index (NFI fit) were examined, values close to 1 are considered to indicate a good fit.

**Results:** No significant correlations were observed for the ADAS-Cog items, ADAS-Cog total score or MMSE total score with the APOE biomarker, and the path associations between ADAS-Cog Total scores and MMSE total scores with biomarkers were not significant ( $p > 0.05$ ). The model that provided the best fit (NFI (0.80) and CFI (0.81)) included change from Week 1 to Week 4 in items of comprehension, word finding, remembering instructions, word recall, as non-significant predictors of and APOE group. The change in comprehension score was 0.52 points higher for APOE carriers than for non-carriers, however results were not significant, and 18% of the variance in the comprehension score was explained by remembering instructions score.

**Conclusions:** Despite studies showing response to treatment and longitudinal cognitive outcome as better in non-carriers of the APOE allele, our results did not show any significant differences in change in APOE group and changes in individual items on the ADAS-Cog, total ADAS-Cog score or MMSE total score. These observations should be replicated by pooling individual trials data and further examination of the contribution of the ADAS-Cog to the assessment of AD.

#### **Learning Objectives:**

- Researchers and mental health professionals will be able to: 1. Identify the cognitive symptoms of Alzheimer's that are commonly measured and assess it's association to the APOE allele.
- Researchers and mental health professionals will be able to: Describe the neurochemical and genetic evidence of Alzheimer's and it's relation to cognitive domains.

**Source of Funding:** ProPhase, LLC

**Literature References:**

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**CEFDINIR FOR NEW ONSET PEDIATRIC NEUROPSYCHIATRIC DISORDERS**

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**Background:** Accumulating evidence suggests that the unexplained acute and dramatic onset of obsessive-compulsive disorder (OCD) and/or tics may be infection or immune precipitated. Pediatric Acute onset Neuropsychiatric Syndrome (PANS) is a subtype of rapid childhood onset OCD and/or tic disorders that begin following an acute infection with accompanying non-focal neurological signs and an episodic course. These symptoms are thought to be precipitated and exacerbated by infections caused by Group A beta-hemolytic *Streptococcus* (GAS), *Mycoplasma pneumoniae*, Influenza, and Lyme disease. Anecdotal reports note symptom improvement in children with PANS after 2-6 weeks of antibiotic treatment. These observations suggest that beta lactam antibiotics may be neuroprotective beyond their antimicrobial efficacy. Our objective was to investigate the use of antibiotic therapy with Cefdinir to reduce clinical severity of symptoms of OCD and/or tics in children with PANS.

**Methods:** Nineteen children ages 4 -13 (average age = 7.4±1.9) were randomized to receive placebo (n=10) or antibiotic (n=9) intervention for the treatment of new onset OCD and/or tics after receiving examinations of family history, diagnostic interview, physical examination, medical record review, and psychological testing. Children randomized to the antibiotic group received 14mg/kg (max 600mg) per day for a total of 30 days, while the placebo received a comparable non-active treatment matched for taste, color and consistency. The primary outcome measures for symptom severity were the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) for OCD, and the Yale Global Tic Severity Scale (YGTSS) for tics.

**Results:** A total of 5 children presented with a diagnosis of OCD only, 8 with tics only, and 6 with a diagnosis of both OCD and tics. There was a decrease in mean for both YGTSS (6.75) and CY-BOCS (8.83) scores in the Cefdinir group following the 30 day treatment regime. Significant group differences were observed for the CY-BOCS scores ( $F(1, 12) = 7.0, p = 0.02$ ), but not for the YGTSS ( $F(1, 13) = 0.88, p = 0.37$ ).

**Conclusions:** The increased mean score in the YGTSS for the placebo group shows an overall worsening of tic symptoms, while the decreasing mean score for the Cefdinir group shows an overall improvement of tics. Furthermore, while the decreased mean scores for the CY-BOCS in both groups shows an improvement of OCD symptoms, the Cefdinir group had a much more significant improvement in OCD symptoms than the group on placebo. In this pilot study, these results suggest that antibiotic therapy may help to reduce the severity of both OCD and tic symptoms in children with PANS. The mechanism of action is presumed to be antimicrobial, immune modulatory or neurochemical. A larger study is warranted.

**Learning Objectives:**

- Compare placebo to antibiotic therapy on changes in overall symptom severity for OCD and/or tics among children with new onset illness.
- Explore the hypothesis that a subset of children experiences the onset of neuropsychiatric disorders in response to a bacterial trigger and continued symptoms may be due to undetected and untreated infections.

**Source of Funding:** 2007 NARSAD Independent Investigator Award by the Brain & Behavior Research Foundation, formerly known as National Alliance for Research on Schizophrenia and Depression (NARSAD).

**Literature References:**

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**EFFECT OF VENLAFAXINE AND DESVENLAFAXINE ON DRUG EFFLUX PROTEIN EXPRESSION AND BIODISTRIBUTION**

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Venlafaxine and its metabolite, desvenlafaxine, are serotonin-norepinephrine reuptake inhibitors both indicated for the treatment of major depressive disorder and venlafaxine a number of anxiety disorders. Previously we observed that venlafaxine, and to a lesser extent desvenlafaxine, induced the expression of the drug efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in whole cells and reduced the cellular permeability of a known drug efflux probe. To validate our in vitro findings, we examined the effect of venlafaxine and desvenlafaxine on drug efflux expression and biodistribution in vivo. Wild-type mice were treated for four consecutive days with 10mg/kg venlafaxine or desvenlafaxine and drug efflux expression was examined in the brain, liver, and intestine. P-gp and BCRP expression was significantly up-regulated in the intestine following treatment with venlafaxine (2.6- and 6.7-fold, respectively) or desvenlafaxine (2.3- and 4.8-fold, respectively). In addition, venlafaxine increased BCRP expression in the brain (40%) and liver (60%), while desvenlafaxine had no effect on drug efflux levels in these tissues. Using the same treatment paradigm, we examined the impact of venlafaxine and desvenlafaxine on the tissue disposition of the known drug efflux probe, topotecan. We observed minimal impact of either drug on the brain disposition of orally administered topotecan. In the periphery, venlafaxine treatment significantly reduced topotecan oral bioavailability by nearly 40%, while the impact of desvenlafaxine on topotecan plasma levels was more modest (23%). These studies demonstrate an effect of venlafaxine on drug efflux transport activity and the potential for clinical drug-drug interactions.

**Learning Objectives:**

- Various agents may increase or decrease the concentrations of other agents via the drug efflux process
- Drug efflux protein effects may cause important drug interactions.

**Source of Funding:** Pfizer, IIR # WS1106613

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**IMPROVING PSYCHOPHARMACOLOGY EDUCATION AND PRACTICE: THE QUANDARY OF GETTING DATA AND INFORMATION TO THE TEACHERS**

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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 residents 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.

**Learning Objectives:**

- Participants will be aware of problems related to getting cutting edge information on new clinical psychopharmacology research.
- Participants will be aware of suggestions to improve the teaching of clinical psychopharmacology.

**Source of Funding:** none

**Literature References:**

- Prabhakar D, Balon R, Zisook S. Assessing the Need for a Multi-Model Curriculum in Psychopharmacology Education – Academic Psychiatry 2012 36:497-499.
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**TREATING ACUTELY AGITATED PATIENTS WITH ASENAPINE SUBLINGUAL TABLETS: A SINGLE-DOSE, RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED TRIAL**

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**Objective:** To describe the efficacy and safety of sublingual asenapine for the treatment of agitation.

**Methods:** This was a double-blind study conducted at a Psychiatric Emergency Department. Agitated adults 18-65 years (any diagnosis) were randomized to receive a single dose of sublingual asenapine 10 mg or placebo. Inclusion criteria included a total score of  $\geq 14$  and at least one individual item score of  $\geq 4$  on the Positive and Negative Syndrome Scale - Excited Component (PANSS-EC). Informed consent was required. The primary outcome measure was change in the PANSS-EC total score from baseline to 2 hours after medication administration. Secondary outcome measures included the proportion of responders as defined by a 40% or greater reduction from baseline on the PANSS-EC total score at 2

hours after medication administration, proportion of responders as defined by Clinical Global Impression-Improvement (CGI-I) scale scores of 'very much' or 'much' improvement at 2 hours after medication administration, and tolerability/safety outcomes as measured by spontaneously reported adverse events and by a Barnes Akathisia Scale assessment at 2 hours after medication administration.

**Results:** A total of 120 subjects were randomized and 60 were allocated to receiving sublingual asenapine 10 mg and 60 were allocated to placebo. The overall study completion rate was 81%, with 93% of asenapine-treated subjects completing vs. 68% for placebo-treated subjects (NNT for completion 4, 95% CI 3-9). Mean baseline PANSS-EC total scores for the asenapine-treated and placebo-treated subjects were  $19.63 \pm 5.29$  and  $20.05 \pm 4.65$  ( $F = 0.21$ , NS), respectively. Mean baseline Clinical Global Impressions-Severity scores for the asenapine-treated and placebo-treated subjects were  $4.98 \pm 0.89$  and  $4.89 \pm 0.99$  ( $F = 0.241$ , NS), respectively. Mean PANSS-EC total scores 2 hours after administration (LOCF) was  $7.86 \pm 5.80$  for the asenapine-treated subjects and  $14.93 \pm 7.24$  for the placebo-treated subjects. Change in the PANSS-EC total score at 2 hours was statistically significantly greater for the asenapine-treated subjects compared to the placebo-treated subjects ( $F=22.50$ ,  $p<0.001$ ). The proportion of subjects categorized as responders at 120 minutes for the asenapine-treated group was 78%, compared with 33% for the placebo-treated group (Chi square = 22.84,  $p < 0.0001$ , NNT 3, 95% CI 2-4). On the CGI-I at 2 hours, 78% of the asenapine group showed 'very much' or 'much' improvement compared to 25% of the control group (Chi Square = 28.40,  $p < 0.0001$ , NNT 2, 95% CI 2-3). BAS scores were a mean of  $1.35 \pm 1.41$  (Questionable) for the asenapine group and  $2.0 \pm 2.26$  (Mild akathisia) for the control group ( $F=3.56$ ,  $p<0.061$ ). The safety/tolerability outcomes were unremarkable.

**Conclusions:** Sublingual asenapine was effective in the treatment of agitation in persons presenting to a Psychiatric Emergency Department. The effect size was comparable to that observed in prior studies of intramuscular olanzapine, ziprasidone, aripiprazole, haloperidol and lorazepam, as well as that for inhaled loxapine.

#### **Learning Objectives:**

- Understand the potential of sublingual asenapine for the treatment of acute agitation, as measured by the PANSS-EC in a randomized double-blind clinical trial.
- To be able to use Number Needed to Treat to indirectly compare sublingual asenapine with other treatments for agitation.

**Source of Funding:** Merck Study Grant 39230

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## **WHITES WITH ADDICTIVE DISORDERS DISCOUNT DELAYED REWARDS LESS STEEPLY THAN THEIR AFRICAN AMERICAN AND HISPANIC COUNTERPARTS**

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Impulsivity is considered a key process underlying addictive behaviors, including alcohol and drug use disorders as well as non-pharmacological addictive behaviors such as problem gambling. Impulsivity can be defined in terms of choices for smaller sooner rewards over larger more delayed rewards, and it may be measured through delay discounting. The term delay discounting refers to the process by which an individual subjectively devalues outcomes as a function of time. Numerous studies have shown that individuals with alcohol and drug use disorders discount delayed outcomes at higher rates (i.e., they are

more impulsive) than controls. Although much emphasis has been given to the examination of discounting in relation to substance-related addictive behaviors, little research has evaluated the relationship between discounting and individual variables, such as race/ethnicity. The little data that exist comparing discounting across racial or ethnic groups are primarily limited to samples of university students, who generally do not have severe patterns of maladaptive behavior. The goal of the current study was to compare the delay discounting rates in the three most common racial/ethnic groups in the United States—Whites, Blacks, and Hispanics. The sample was comprised of a large number of individuals with problem gambling ( $n = 315$ ), an addictive behavioral pattern that does not confound the behavior with physiological effects. Participants completed questionnaires about discounting of hypothetical monetary outcomes. The discounting questionnaire was comprised of choices between a smaller monetary outcome delivered immediately versus a larger monetary outcome delivered at a later point in time. Hyperbolic discounting functions were used to estimate the rates of delay discounting based on participants' responses obtained through the questionnaires. Results showed statistically significant effects of race/ethnicity on delay discounting rates. White problem gamblers discounted delayed monetary outcomes less steeply than their African American and Hispanic counterparts, even after controlling for substance use, education, and other variables. These results suggest that among those individuals who develop problem gambling, Whites are less impulsive than African Americans and Hispanics—at least in terms of making intertemporal choices. These data suggest that race and ethnicity should be regarded more carefully when analyzing differences in discounting, and possibly when examining impulsivity at more global levels.

#### **Learning Objectives:**

- Summarize the relationship between delay discounting with substance use and gambling problems.
- Explain the relationship between discounting rate across race/ethnic groups and the development of addictive-related behaviors.

#### **Source of Funding:**

Funding for this study and preparation of this report was provided in part by NIH grants P30-DA023918, R01-DA027615, R01-DA022739, R01-DA021567, R01-DA13444, P50-DA09241, P60-AA03510, R01-HD075630, and T32-AA07290.

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### **INCIDENCE OF TARDIVE DYSKINESIA: A COMPARISON OF LONG-ACTING INJECTABLE AND ORAL PALIPERIDONE**

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**Objective:** To estimate the incidence of tardive dyskinesia (TD) in long-term studies of once-monthly injectable paliperidone palmitate (PP) and oral paliperidone (Pali ER) using Schooler-Kane criteria and spontaneously reported adverse events (AE).

**Methods:** Patient level data were pooled from completed schizophrenia and bipolar studies (four PP [N=1689] and six Pali ER [N=2668]) of  $\geq 6$  months duration that included Abnormal Involuntary Movement Scale (AIMS) assessments. Cases of TD based upon Schooler-Kane criteria defined for probable TD and persistent TD were determined using AIMS total score (items 1-7). Patients scoring  $\geq 2$

on two or more items or  $\geq 3$  on at least one item were considered to have qualifying scores for either probable or persistent TD. Probable TD cases included patients with qualifying AIMS scores for  $\geq 3$  months, and persistent TD cases included those patients with qualifying AIMS score persisting for an additional 3 months ( $\geq 6$  months total). Subjects were exposed to study medications through the entire assessment period. Adverse event reports of TD were summarized. TD incidence was calculated in treatment-emergent cases only. Impact of duration was assessed by summarizing the monthly incidence rate of dyskinesias with AIMS total score  $\geq 3$ .

**Results:** In schizophrenia studies, TD incidence was reported for PP (N=1689) vs. Pali ER (N=2054), respectively as: AE, 0.18% vs. 0.10%; probable, 0.01% vs. 0.19%; and persistent, 0.01% vs. 0.05%. In bipolar studies (Pali ER only [N=614]), TD incidence was zero (for spontaneous AE reporting, probable and persistent TD). Incidence of dyskinesias (total AIMS score  $\geq 3$ ) was highest within the first month of treatment with both formulations (PP: 13.1%; Pali ER: 11.7%) and steadily decreased over time (for months 6-7: PP: 5.4%; Pali ER: 6.4%).

**Conclusions:** In this post-hoc analysis, risk of TD and incidence of dyskinesias was similar between PP and Pali ER treatments. Long-Term TD risk appeared to be similar regardless of route of administration. Longer cumulative exposure did not appear to increase dyskinesia risk.

**Learning Objectives:**

- Compare incidence of tardive dyskinesia with oral paliperidone long-term studies to paliperidone LAI studies
- Review tardive dyskinesia criteria using Schooler-Kane methods

**Source of Funding:** The study was funded by Janssen Scientific Affairs, LLC, Raritan, N.J., USA, a Johnson & Johnson company.

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**EFFECT OF LURASIDONE ON WEIGHT AND METABOLIC PARAMETERS: A COMPREHENSIVE ANALYSIS OF SHORT- AND LONG-TERM TRIALS IN SCHIZOPHRENIA**

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**Objectives:** Patients with schizophrenia are at significantly higher risk for diabetes, dyslipidemia, hypertension, and obesity, which all contribute to increased mortality compared with the general population. Antipsychotic medication may add further cardiometabolic risk, with significant differences reported among atypical antipsychotics in effects on weight, glucose and lipids. The aim of the current pooled analysis of double-blind short-term and open-label longer-term studies was to evaluate the effect of lurasidone on weight and metabolic parameters.

**Methods:** Short-term data were pooled from seven double-blind, placebo-controlled, 6-week treatment studies of patients who met DSM-IV criteria for schizophrenia with an acute exacerbation. The short-term safety analysis sample consisted of patients treated with lurasidone (dose range, 20-160 mg, total N=1508); haloperidol 10 mg (N=72); olanzapine 15 mg (N=122); risperidone 4 mg (N=65); quetiapine XR 600 mg (QXR; N=119); and placebo (N=708). Longer-term data (6-22 months) were pooled from open-label studies in patients taking lurasidone 40-120 mg/day.

**Results:** In the short-term treatment sample, the proportion experiencing  $\geq 7\%$  weight gain was 4.8% for combined lurasidone, 4.2% for haloperidol, 34.4% for olanzapine, 6.2% for risperidone, 15.3% for QXR, and 3.3% for placebo. Median endpoint change in lipids were as follows: triglycerides (mg/dL), -4.0 for



combined lurasidone, -3.0 for haloperidol, +25.0 for olanzapine, +4.0 for risperidone, +9.5 for QXR, and -6.0 for placebo; total cholesterol (mg/dL), -5.0 for combined lurasidone, -8.0 for haloperidol, +9.0 for olanzapine, +6.5 for risperidone, +6.0 for QXR, and -5.0 for placebo; similar trends were recorded for changes in LDL for lurasidone, QXR and olanzapine. Median glucose (mg/dL) was unchanged (LOCF-endpoint) for combined lurasidone (0.0) and placebo (0.0), and somewhat higher for haloperidol (+2.0), olanzapine (+4.0), risperidone (+3.0), and QXR (+3.0). Minimal-to-no changes were observed at Week 6 LOCF-endpoint in HbA1c. In the longer-term treatment sample, mean change in weight at Month 12 was -0.59 kg for the combined lurasidone treatment group (observed case); and the median changes in metabolic parameters at Month 12 were: -0.08 nmol/L for total cholesterol and -0.06 nmol/L for triglycerides (observed case).

**Conclusions:** In this comprehensive analysis of short- and longer-term studies, treatment with lurasidone was associated with minimal increases in weight and BMI in short-term trials, and small decreases in weight and BMI in longer-term trials. In the combined lurasidone dosage groups there was a baseline-to-endpoint decrease in mean total and LDL cholesterol, and triglycerides during both short-term and longer-term treatment.

#### **Learning Objectives:**

- At the conclusion of the presentation, participants will have a better understanding of the comparative effect of short-term treatment of schizophrenia with lurasidone and other antipsychotics on weight and metabolic parameters
- At the conclusion of the presentation, participants will have a better understanding of the comparative effect of long-term treatment of schizophrenia with lurasidone and other antipsychotics on weight and metabolic parameters

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

#### **Literature References:**

- Meyer JM. Antipsychotics and metabolics in the post-CATIE era. *Curr Top Behav Neurosci*. 2010;4:23-42.
- Mitchell AJ et al. Prevalence of Metabolic Syndrome and Metabolic Abnormalities in Schizophrenia and Related Disorders—A Systematic Review and Meta-Analysis *Schizophr Bull* first published online December 29, 2011 doi:10.1093/schbul/sbr148

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### **CARIPRAZINE IN ACUTE EXACERBATION OF SCHIZOPHRENIA: A FIXED-DOSE PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED TRIAL**

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**Objective:** Cariprazine (CAR), an orally active and potent dopamine D<sub>3</sub>/D<sub>2</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors, is in development for the treatment of schizophrenia and bipolar mania. CAR has demonstrated efficacy in patients with schizophrenia in Phase II (NCT00694707) and Phase III (NCT01104779) studies. This Phase III trial (NCT01104766) further evaluated the efficacy, safety, and tolerability of CAR in patients with acute exacerbation of schizophrenia.

**Methods:** This was an international, double-blind, placebo (PBO)- and active-controlled, fixed-dose study of 9 weeks duration (up to 7-day washout, 6-week double-blind treatment, 2-week safety follow-up). Patients with schizophrenia (minimum of 1 year; current episode <2 weeks) were randomized to CAR 3 mg/d, CAR 6 mg/d, aripiprazole (ARI) 10 mg/d (active control), or PBO. Patients were hospitalized at screening and for at least 4 weeks of double-blind treatment. Primary efficacy parameter was change from baseline to Week 6 in PANSS total score analyzed using a mixed-effects model of repeated measures (MMRM) and adjusting for multiple comparisons; secondary efficacy parameter was change from baseline in Clinical Global Impressions-Severity (CGI-S) score. Safety was evaluated by adverse events (AEs), laboratory values, vital signs, ophthalmology assessments, electrocardiograms

(ECGs), and extrapyramidal symptom (EPS) scales.

**Results:** A total of 617 patients were randomized and received treatment (PBO, 153; CAR 3 mg/d, 155; CAR 6 mg/d, 157; ARI, 152) (Safety Population); 66% completed the study. Change from baseline to Week 6 on PANSS total score was significantly greater for both CAR groups vs PBO (LSMD vs PBO: CAR 3 mg/d=-6.0,  $P=.0044$ ; CAR 6 mg/d=-8.8,  $P<.0001$ ); both CAR groups also showed significantly greater improvement on CGI-S scores relative to PBO (LSMD: CAR 3 mg/d=-0.4,  $P=.0044$ ; CAR 6 mg/d=-0.5,  $P<.0001$ ). ARI was significantly superior to PBO on both measures (LSMD: PANSS=-7.0,  $P=.0008$ ; CGI-S=-0.4,  $P=.0001$ ; not adjusted for multiple comparisons). Treatment-emergent AEs (TEAEs) were reported in 67%, 61%, 71%, and 66% of PBO, CAR 3 mg/d, CAR 6 mg/d, and ARI patients, respectively. Common TEAEs ( $\geq 5\%$  and twice the rate of PBO) were akathisia in the CAR 6 mg/d group, and abdominal discomfort and nausea in the ARI group; most TEAEs were mild to moderate in severity. Patients in the CAR and ARI groups relative to PBO had greater EPS (parkinsonism) and akathisia as determined by SAS and BARS, respectively.

**Conclusion:** CAR 3 mg/d and 6 mg/d demonstrated significant improvement relative to PBO on PANSS total score and CGI-S. CAR was generally well tolerated, although the incidence of EPS and akathisia was greater for CAR than PBO.

**Learning Objectives:**

- Evaluate the efficacy of cariprazine 3mg/d and 6 mg/d in the treatment of schizophrenia
- Understand the safety and tolerability profile of cariprazine in patients with schizophrenia

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

**Literature References:**

- Kiss B, Horváth A, Némethy Z, Schmidt E, Laszlovszky I, Bugovics G, Fazekas K, Hornok K, Orosz S, Gyertyán I, Agai-Csongor E, Domány G, Tihanyi K, Adham N, Szombathelyi Z: Cariprazine (RGH-188), a dopamine D3 receptor-preferring, D3/D2 dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. *J Pharmacol Exp Ther*. 2010;333(1):328-340.
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**USE OF ITEM RESPONSE ANALYSIS TO IDENTIFY AN INTEGRATED NEGATIVE SYMPTOM FACTOR OF THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)**

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**Background:** The assessment and treatment of negative symptoms continues to be a major challenge for mental health care in schizophrenia. Negative symptoms are a core feature of schizophrenia and have significant predictive value for patients' cognitive, social and community functioning. The aim of this study was to first, systematically review published Principle Components (PCA) and negative factor structures of the PANSS, and to extract a set of items most frequently included in the negative symptom domain, and secondly, to examine the quality of these identified items using item analysis techniques and non-parametric Item Response Theory (IRT) in order to address which items of the PANSS best represent an observable dimension (or dimensions) of negative symptoms.

**Methods:** Five steps were chosen in order to select relevant negative items for an Integrated Negative Factor: First, 22 factor analysis and PCA met the criteria for inclusion. Second, using a large dataset ( $n = 7,187$ ); we extracted all items loading on one or more the 22 selected PCA. Third, PCA was performed on the selected items loading on the negative factor or domain. Items not loading with a value of  $\geq 0.5$ , or loading on more than one component with values of  $\geq 0.5$  were discarded. Fourth, items identified

through PCA were included in a non-parametric IRT analysis. Finally, the items best fitting the construct of negative symptoms were selected (based on Option (OCC) and Item Characteristic Curves (ICC)).

**Results:** Of the 22 articles examined, there were a total of 15 items that loaded on the negative symptom domain in at least one study. Emotional Withdrawal loaded on the negative dimension for all studies. Principle Components analysis, with no rotation, of 7,187 patients revealed three components. Items with loadings of 0.5 or higher were assigned to the Integrated Negative Factor and included: Poor Attention, Disturbance of Volition, Active Social Avoidance, Motor Retardation, Blunted Affect, Emotional Withdrawal, Poor Rapport, Passive/Apathetic Social Withdrawal, Difficulty in Abstract Thinking, Lack of Spontaneity and Flow of Conversation, Stereotyped Thinking. Non-parametric IRT revealed an Integrated Negative Symptom Factor which includes Emotional Withdrawal, Blunted Affect, Passive/Apathetic Social Withdrawal, Poor Rapport, Lack of Spontaneity and Conversation Flow, Active Social Avoidance, Disturbance of Volition, Stereotyped Thinking and Difficulty in Abstract Thinking.

**Conclusions:** This is the first study to use Item Response Analysis to arrive at a set of psychometrically valid negative symptom items. Because there is still debate on effective treatments for negative symptoms in schizophrenia, clarifying whether negative symptoms can be better characterized by a set of PANSS items, as our study suggests, carries significant clinical implications.

#### **Learning Objectives:**

- By systematically examining the various published Principle Components (PCA) factor structures of PANSS negative factors and by examining the quality and functioning of the identified negative items using non-parametric Item Response Theory (IRT) it may be possible to determine the best selection of negative symptom items, which better reflect underlying pathophysiological etiologies and allow for more accurate testing of therapeutic intervention.
- While factor analytic studies shed light on the underlying structure of a symptom domain, they do not address the specific item functioning, or the quality of the included item. In order to examine these aspects for negative items, Item Response Theory (IRT) can be very helpful. Applications of IRT will be presented.

**Source of Funding:** This project did not receive any funding.

#### **Literature References:**

- Khan A, Lewis C, Lindenmayer JP. Use of non-parametric item response theory to develop a shortened version of the Positive and Negative Syndrome Scale (PANSS). *BMC Psychiatry*. 2011 Nov 16;11:178.
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### **IMPACT OF SWITCHING FROM ORAL TO LONG-ACTING INJECTABLE ANTIPSYCHOTIC MEDICATIONS AMONG MEDICAID INSURED PATIENTS WITH SCHIZOPHRENIA**

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**Background:** Although long-acting injectable (LAI) antipsychotics have been available in clinical practice for many years, they remain underutilized among patients with low adherence to oral antipsychotic medications [1, 2].

**Objective:** To evaluate healthcare resource utilization and direct medical costs before vs. after switching from oral antipsychotics to LAI antipsychotics among Medicaid patients with schizophrenia.

**Methods:** Adult patients with schizophrenia ( $\geq 18$  years of age) with at least 1 inpatient claim or 2 outpatient claims on separate dates with a primary or secondary diagnosis of ICD-9-CM code 295.X before initiating treatment with LAI antipsychotics (index event) were identified for inclusion from the *MarketScan® Research* database (1/1/2006-12/31/2010). Patients were required to have 12 months of continuous Medicaid health plan enrollment before (baseline period) and after (follow-up period) the LAI antipsychotic initiation. Patients were further required to have received at least one oral antipsychotic medication prior to initiating LAI antipsychotics. Healthcare resource utilization and associated actual direct medical costs were compared before and after LAI initiation.

**Results:** Of 2,883 schizophrenia patients who switched from oral to LAI antipsychotics, mean age was 39.9 years and 52% were male. The LAI antipsychotics initiated included risperidone (41.6%), haloperidol (39.2%), fluphenazine (11.9%), and paliperidone (7.4%). After initiation of LAIs, a decline was observed from the baseline period to the follow-up period in key economic outcomes such as: all cause hospitalizations ( $1.41 \pm 2.26$  vs.  $0.98 \pm 2.01$ ,  $p < 0.001$ ), schizophrenia-related hospitalizations ( $1.12 \pm 1.66$  vs.  $0.81 \pm 1.74$ ,  $p < 0.001$ ), annual total hospitalization days (all cause:  $12.74 \pm 21.65$  vs.  $8.38 \pm 21.11$  days,  $p < 0.001$ ) and schizophrenia-related hospitalization days ( $10.56 \pm 17.48$  vs.  $7.13 \pm 18.40$  days,  $p < 0.001$ ). As a result, hospital payments were significantly lower during the follow-up period (all cause:  $\$16,238 \pm \$30,144$  vs.  $\$11,713 \pm \$30,407$ ,  $p < 0.001$ ; schizophrenia-related:  $\$13,109 \pm \$23,698$  vs.  $\$9,573 \pm \$26,241$ ,  $p < 0.001$ ).

**Conclusion:** Among Medicaid insured patients with schizophrenia, there is a reduction in all-cause and schizophrenia related hospitalizations and hospital days after initiation of LAI antipsychotics, which is also reflected in reductions in inpatient direct medical costs. These results provide naturalistic setting evidence on the utility of LAIs in reducing total and schizophrenia-related hospitalizations and associated medical costs among Medicaid patients with schizophrenia.

**Learning Objectives:**

- To evaluate how Medicaid insured patients with schizophrenia respond to switching from an oral to a LAI antipsychotic
- To determine whether switching to a LAI antipsychotic is associated with better disease management

**Source of Funding:**

Otsuka America Pharmaceutical, Inc. and H. Lundbeck A/S

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2. Zhornitsky S, Stip E. Oral versus Long-Acting Injectable Antipsychotics in the Treatment of Schizophrenia and Special Populations at Risk for Treatment Nonadherence: A Systematic Review. *Schizophr Res Treatment*. 2012; 2012: 407171

**INSIGHT, TREATMENT OUTCOMES AND RECOVERY IN FIRST-EPISODE SCHIZOPHRENIA**

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**Objective:** The objective of this study was to investigate relationships between insight and cognitive performance, social functioning, and subjective quality of life rating in patients with first-episode schizophrenia who had attained symptom remission.

**Methods:** The study sample consisted of two patient cohorts with first-episode schizophrenia (N=34 in Cohort 1, N=31 in Cohort 2), aged 18-35 years and had treatment for

**Results:** All but 3 patients met criteria for symptom remission. Patients demonstrated good levels of

insight (SAI total =11.4, SD=2.6), and the mean BACS composite z-score was -2.05 (SD=1.27). The overall median SOFAS score was 50 (IQR 45 to 60), indicating moderate to serious impairment in social and occupational functioning in a majority of patients. Patients also experienced marked functional impairment, being significantly lower on social engagement, interpersonal communication, recreation, pro-social, and employment SFS domains compared to normal controls ( $p<0.05$ ). There was a significant correlation between the overall SAI insight score and G12 of PANSS (lack of judgement and insight,  $p<0.05$ ). Higher level of insight was associated with increased cognitive performance, verbal memory and processing speed (all  $p<0.05$ ). Level of insight into illness was inversely related to both Interpersonal Communication (an objective SFS domain,  $p<0.05$ ) and lower Social Relationship (a subjective WHOQOL-BREF domain,  $p<0.05$ ).

**Discussion:** Our findings suggest that despite good insight, symptom remission and lack of depression, there is significant impairment in neurocognitive and social functioning in first-episode schizophrenia. Higher levels of insight were associated with better cognitive performance.

**Learning Objectives:**

- To learn interrelationships between insight and cognitive performance, social functioning, and subjective quality of life rating in patients with first-episode schizophrenia who had attained symptom remission.
- To learn the impact of illness awareness on treatment outcomes.

**Source of Funding:** N/A

**Literature References:**

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- Addington J., Addington D., 2000. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophr. Res.* 44(1), 47-56.

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**CHARACTERIZATION OF SUBJECTS WITH SCHIZOPHRENIA AND CRIMINAL JUSTICE SYSTEM INVOLVEMENT FROM AN ONGOING CLINICAL TRIAL**

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**Introduction:** Overrepresentation of people with serious mental illness in the US criminal justice system (CJS) is an important public health concern. A recent analysis of the CATIE study identified risk factors for CJS involvement among schizophrenia subjects such as younger age, male sex, adolescent conduct disorder diagnosis, symptoms of akathisia, and drug abuse (Greenberg et al, *Community Ment Health J.* 2011;47:727-736). This analysis characterizes the population enrolled in an ongoing prospective study of schizophrenia subjects recently involved with the CJS and compares the prevalence of these risk factors and other variables with those from CATIE.

**Methods:** Paliperidone Research in Demonstrating Effectiveness (PRIDE; NCT01157351) is an ongoing, 15-month, randomized, open-label, rater-blinded, parallel-group, multicenter US study comparing paliperidone palmitate with oral antipsychotics in a community sample of subjects with schizophrenia recently released from incarceration. Baseline demographics and clinical characteristics of subjects enrolled (as of 8/21/12) in PRIDE were compared with published results from the overall CATIE population (Lieberman et al, *N Engl J Med.* 2005;353:1209-1223; Miller et al, *Br J Psychiatry.* 2008;193:279-288).

**Results:** Corresponding baseline data were available for several variables in both PRIDE (n=413) and CATIE (n=1460). Data for potential risk factors for CJS involvement identified by Greenberg et al were (PRIDE vs CATIE):

1. Mean (SD) age: 38.0 (10.5) vs 40.6 (11.1) years
2. Male sex: 87.1% vs 74.0%

3. Akathisia: 16.8% (via ESRS-A scale) vs 19.9% (via BARS scale)
4. Substance abuse (alcohol and drug combined): 54.4% (via ASI-LITE) vs 37.2% (via Swartz et al, *Psychiatr Serv.* 2006;57:1110-1116)
5. Adolescent conduct disorder diagnosis was not available from PRIDE.

Other variables for which data were available (PRIDE vs CATIE) included:

1. African American: 62.6% vs 35.1%
2. Mean (SD) age at first treatment for behavioral/emotional problems: 20.7 (7.4) vs 24.0 (8.9) years
3. Mean (SD) length of illness: 16.8 (10.1) vs 14.4 (10.7) years
4. Mean (SD) CGI-S score: 3.8 (0.8) vs 4.0 (0.9)
5. Percent unemployed: 86.9% vs 84.9%

**Conclusion:** Data suggest differences in several baseline characteristics between schizophrenia subjects identified in a study evaluating recently incarcerated schizophrenic persons and those identified through a more general study of persons with schizophrenia. These findings may help characterize clinical and phenotypic features associated with CJS involvement among persons with schizophrenia.

#### **Learning Objectives:**

- To educate participants on the incidence of psychiatric disorders within the criminal justice system
- To characterize patients with schizophrenia recently involved with the criminal justice system, which may inform generalizability of findings in this population to the overall schizophrenia population

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

#### **Literature References:**

- Steadman HJ, Osher FC, Robbins PC, Case B, Samuels S. Prevalence of serious mental illness among jail inmates. *Psychiatr Serv.* 2009;60(6):761-765
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## **MULTIPLE OBESITY-RELATED GENES ARE ASSOCIATED WITH ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN DRUG NAÏVE PEDIATRIC PATIENTS**

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**Background:** Weight gain is a common and serious side effect of antipsychotic drugs (APD). Recent work from our group found that variants near the melanocortin 4 receptor (*MC4R*) gene significantly predicted antipsychotic-induced weight gain (Malhotra et al. 2012), and *MC4R* is a known risk gene for obesity in the general population. We hypothesized that the risk genes in the general population may also be risk genes for antipsychotic-induced weight gain. We used the genes that are associated with obesity in the general population as candidate genes, and examined whether they are significantly associated with antipsychotic-induced weight gain in a drug-naïve pediatric sample. The statistical power may be enhanced in detecting significant genetic signals in pharmacogenetic studies.

**Methods:** Review of the published genome-wide association studies (GWAS) of obesity or body mass index (BMI) in the general population revealed that 69 single nucleotide polymorphisms (SNPs) from 44 genes/regions reached genome-wide significance ( $p < 5 \times 10^{-8}$ ). Our sample consisted of 139 drug-naïve pediatric patients undergoing treatment with APD (risperidone, quetiapine, and aripiprazole) for 12 weeks (58.3% male, 77% Caucasian, mean age =  $13.38 \pm 3.75$  years). Patients were genotyped using the Illumina Omni-1Quad platform. 68 out of the 69 candidate SNPs (from 43 genes/regions) were either directly genotyped or had proxy SNPs in our dataset. Separate association studies were performed on each of the 68 SNPs in additive, recessive, and dominant models. For genes/regions that have multiple SNPs, one was selected based on LD to represent the gene/region. Change in BMI from baseline to 12 weeks was the phenotype. Significance level was set at  $p < 0.05$ .

**Results:** Out of 43 association tests (43 SNPs in additive, dominant, and recessive models, i.e.,  $43 \times 3 = 129$ ), 10 were significant at  $p < 0.05$  level ( $10/43 = 23.3\%$ ). This was significantly more than what is expected by chance,  $p < 0.0001$ . These genes are: MC4R, TFAP2B, TRNASUP6P-NRXN3, POC5, NUDT3, KCNMA1, FTO, STK33, RPL28P3-RPSAP37, and MTCH2. Each SNP was examined in our data to determine whether risk alleles were consistent with the original publications. Out of 68 SNPs, 44 were consistent and 24 were not. Out of 43 genes/regions, 28 were consistent and 15 were not. These were more than what is expected by chance,  $p < 0.05$  (binomial test).

**Discussion:** Some risk genes of obesity in the general population appear also to be risk genes of antipsychotic-induced weight gain. Due to its within-subject design in pharmacogenetic studies, enhanced statistical power resulted in significant genetic findings in relatively small samples. Pharmacogenetics may be at a particular advantage of identifying genes for complex traits with considerable and variable environmental contributions. Further studies are needed to elucidate the biological mechanisms of antipsychotic-induced weight gain.

#### **Learning Objectives:**

- To understand the genetic risk factors of antipsychotic-induced weight gain
- To learn how genetic risk factors of obesity in general population are related to antipsychotic-induced weight gain

**Source of Funding:** NARSAD Young Investigator Award to Jianping Zhang, MD, PhD.

#### **Literature References:**

- Malhotra AK, Correll CU, Chowdhury NI, et al. Association Between Common Variants Near the Melanocortin 4 Receptor Gene and Severe Antipsychotic Drug-Induced Weight Gain. *Arch Gen Psychiatry*. 2012;69(9):904-912.
- Zhang JP, Malhotra AK. Pharmacogenetics and antipsychotics: Therapeutic efficacy and side effects prediction. *Expert Opin Drug Metab Toxicol*. 2011;7(1):9-37.

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### **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF ALKS 3831 IN THE PREVENTION OF OLANZAPINE-INDUCED WEIGHT GAIN IN HEALTHY MALE VOLUNTEERS**

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**Purpose:** To investigate the safety and effect on weight of ALKS 3831 (olanzapine 10 mg + the opioid modulator ALKS 33 [5 mg]) in comparison to olanzapine in healthy, normal weight male volunteers.

**Methods:** A Phase I, multicenter, randomized, double-blind, placebo-controlled study was conducted. Subjects with normal, stable body weight were randomized to olanzapine (10 mg), ALKS 3831, ALKS 33 (5 mg), or placebo (PBO) in a 2:2:1:1 ratio. After 21 days of daily dosing, subjects were observed off treatment for 14 days. Efficacy was determined by the change from baseline to last treatment period assessment in body weight (kg) for olanzapine vs. ALKS 3831. Mann-Whitney-Wilcoxon tests were used for pairwise comparisons. Safety monitoring included adverse events (AEs), vital signs, and laboratory testing.

**Results:** One hundred and six males (18-33 yrs) were randomized to: olanzapine (n=35), ALKS 3831 (n=34), ALKS 33 (n=20), or PBO (n=17). At baseline, subjects' weight ranged from 49.5-86.0 kg and BMI ranged from 17.9-25.2 kg/m<sup>2</sup>. After 3 weeks of daily dosing, the absolute mean (SD) change from baseline in body weight was: olanzapine: +3.4 (±1.8); ALKS 3831: +2.5 (±1.4); ALKS 33: +0.7 (±2.5); and PBO: +0.8 (±1.4) kg. Weight gain differences were significant for: olanzapine vs. ALKS 3831 ( $p < 0.014$ ); olanzapine vs. PBO ( $p < 0.001$ ) and ALKS 3831 vs. PBO ( $p < 0.001$ ), but not for ALKS 33 vs. PBO ( $p = 0.206$ ). Counts (%) for common AEs for olanzapine, ALKS 3831, ALKS 33, and PBO were:

Orthostatic hypotension or tachycardia: 13 (37.1%), 11 (32.4%), 2 (10%) and 0;

Somnolence: 7 (20%), 8 (3.5%), 1 (5%), and 0;

Elevated liver function tests: 5 (14.4%), 7 (20.6%), 0, and 0; and Nausea: 2 (5.7%), 3 (8.8%), 5 (25%), and 1 (5.9%), respectively.

**Conclusions:** ALKS 3831 was associated with significantly less weight gain vs. olanzapine and less nausea than ALKS 33 alone. Overall safety and tolerability of ALKS 3831 was similar to olanzapine alone. ALKS 3831 may offer effective treatment of psychosis with less metabolic risk. Given these significant Phase I findings, further research is warranted to explore additional doses over longer durations in treatment populations.

**Learning Objectives:**

- Attendees will understand the design of a Phase I trial to determine the impact on antipsychotic weight gain when adding the novel opioid modulator, ALKS 33, to olanzapine.
- Attendees will understand the impact of adding ALKS 33 to olanzapine in terms of ameliorating weight gain and safety.

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

**Literature References:**

- Todtenkopf MS, Dean RL, Brunner MJ, Knopp M, Deaver DR. The Novel Opioid Receptor Modulator RDC-0313 (ALKS 33) Reduces Olanzapine-Induced Weight Gain and Adipose Accretion in a Novel Nonhuman Primate Model of Antipsychotic-Related Weight Changes. ACNP 2011: Hot Topics and poster presentation, III-206.
- Topics and poster presentation, III-206. Todtenkopf MS, O'Neill KS, Kelly SM, Richie KA, Dean RL, Eyerman, DE, Deaver DR. RDC-0313 (ALKS 33), a Novel Opioid Receptor Modulator, Reduces Olanzapine-Induced Weight Gain in Female Rats. ACNP 2010: III-81

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**USING MAGNETOENCEPHALOGRAPHY TO PROBE THE MULTISENSORY BENEFIT IN PATIENTS WITH SCHIZOPHRENIA**

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<sup>1</sup>The Mind Research Network

**Background:** Deficits in the auditory and visual pathways have now been widely reported in patients with schizophrenia. Based on the dysconnectivity hypothesis in schizophrenia (Friston 1995), we hypothesized that patients with schizophrenia would experience further deficits in multisensory processing. In contrast, our previous results (Stone et al. 2011) show that patients with schizophrenia benefit when presented with multisensory relative to unisensory stimuli. In the current study we extend our previous electroencephalography (EEG) study to a larger magnetoencephalography (MEG) study. We hypothesized that a subset of patients with schizophrenia will benefit from multisensory stimulation and MEG can accurately identify cortical locations related to this multisensory compensatory response.

**Methods:** We studied 63 schizophrenia patients (SP) and 67 age-matched healthy control (HC) participants. During MEG data collection (306 channel Elekta Neuromag), participants were presented with visual (V), auditory (A), and synchronous (AV) stimuli. The visual stimuli consisted of soccer balls (small or large) presented in a perspective drawing of a soccer field, either upfield (Near) or down-field (Far) relative to the participant. The auditory stimuli were either loud (near) or quiet (far). Participants performed a two-choice reaction time task, deciding if the stimulus (A, V or AV) was near or far with a button press. The A, V and AV stimuli were presented randomly. Source analysis was performed on the MEG data to identify the location and timing of the cortical activity elicited by the task.

**Results:** Our results show facilitation of the AV reaction time relative to either of the unisensory (A or V) reaction times in the SP group only, similar to our previous EEG study. A cluster analysis identified three clusters. One cluster consisting of primarily SP showed the greatest multisensory benefit although these patients showed significantly lower performance outcomes (3 MATRICS subscales  $p$ 's < 0.01) than the other cluster groups. However, there were no significant differences in symptom severity across groups. Also, in a subset of subjects, we identified group differences in the MEG source time-courses (posterior superior temporal sulcus showed a delayed response in SP in the unisensory, but not in the multisensory condition – significant interaction  $p=0.048$ ).



**Conclusions:** Interestingly, the cluster group with the poorest functional outcome achieved the greatest gain from multisensory stimuli, suggesting that even the more severely affected patients can elicit compensatory brain responses. These compensatory mechanisms appear to in part originate in posterior temporal cortex. Combining these results provides a more comprehensive understanding of the regions that help compensate for unisensory deficits in SP. These regions may be useful targets for brain stimulation techniques.

**Learning Objectives:**

- Using MEG to identify differences in brain function in patients with schizophrenia relative to healthy controls.
- Illustrate the multisensory benefit in patients with schizophrenia and how that relates to physiological and functional outcome measures.

**Source of Funding:** NIH NIGMS #8P20GM103472 and and NCRR #5P20RR021938

**Literature References:**

- Friston KJ; Frith CD: Schizophrenia: a disconnection syndrome? Clin Neurosci 1995; 3:89-97.
- Stone DB; Urrea LJ; Aine CJ; Bustillo JR; Clark VP; Stephen JM: Unisensory processing and multisensory integration in schizophrenia: a high-density electrical mapping study. Neuropsychologia 2011; 49:3178-3187.

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**GENETIC PREDICTORS OF ANTIPSYCHOTIC PHARMACOKINETICS AND PHARMACODYNAMICS**

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Antipsychotics have a high rate of discontinuation due to inefficacy and/or adverse effects. An ancillary study to the CATIE trials aimed to identify and quantify sources of variability in the clearance of antipsychotics. We have previously shown that sex and smoking are associated with differential clearance of several antipsychotics (Bigos et al. *J Clin Pharmacol* 2008;48(2):157-165). We are currently using pharmacokinetic and genetic data from the CATIE schizophrenia trial to identify genetic predictors of antipsychotic pharmacokinetics using non-linear mixed effects modeling

A candidate gene approach has identified several genetic variants in cytochrome P450 genes that highly predict the clearance of antipsychotics. We have shown that CYP3A43 significantly predicts clearance of olanzapine (Bigos et al. *Molecular Psychiatry* 2011; 16:620-625). We have recently found that the same SNP in CYP3A43 also significantly predicts 30% of risperidone clearance. Of the 230 SNPs in CYP450s, the CYP3A43 SNP (rs472660) was the most significantly associated with both risperidone and olanzapine clearance, and predicted most and the entire previous race effects in drug clearance, respectively. African Americans have a greater proportion of carriers of the fast metabolizing allele. This CYP3A43 SNP did not predict either quetiapine or ziprasidone, which was predicted based on the lack of racial effects on their clearance. The most significant predictors of ziprasidone and quetiapine clearance were SNPs located in the CYP2A/2B families of genes on chromosome 12. SNPs in other CYP gene families were also associated with clearance of one or more of the antipsychotics.

We are also conducting a GWA study using the original CATIE Affy 500K chip, and we have identified novel genetic predictors, which have not previously been associated with drug metabolism, including ST6GAL1 which best predicts olanzapine clearance. A long-term goal is to use these genetic variants to build models of predictors of antipsychotic drug metabolism in order to guide dosing. A separate goal is to use the variability in antipsychotic clearance as a covariate in studies designed to identify genetic predictors of antipsychotic drug response. We have shown that patients with schizophrenia who carry the risk allele for KCNH2, are 5-times less likely to discontinue olanzapine, only after controlling for differences in olanzapine clearance (Apud et al. *Am J Psychiatry*. 2012;169:725-734). The overall goal of this research is to use genetics to identify and characterize sources of variability in pharmacokinetics and response to psychotropics in order to optimize treatment strategies.

**Learning Objectives:**

- To learn how variability in the pharmacokinetics of antipsychotics affects clinical response.
- To be able to identify genes that predict differences in the pharmacokinetics of antipsychotics.

**Source of Funding:** Lieber Institute for Brain Development

**Literature References:**

- Bigos KL, Pollock BG, Coley KC, Marder SR, Miller DD, Kirshner MA, Bies RR. Sex, Race, and Smoking Impact Olanzapine Exposure. *J Clin Pharmacol* 2008; 48(2):157-165.
- Apud, JA, Zhang, F, Decot, H, Bigos KL, Weinberger DR. Genetic variation in *KCNH2* associated with expression in brain of a unique Herg isoform modulates treatment response in patients with schizophrenia. *Am J Psychiatry*. 2012;169:725-734
- Bigos KL, Bies RR, Pollock BG, Lowy JJ, Zhang F, Weinberger DR. Genetic Variation in CYP3A43 Explains Racial Difference in Olanzapine Clearance. *Molecular Psychiatry*. 2011; 16:620-625.

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**EVALUATION OF HEALTH RELATED QUALITY OF LIFE OUTCOMES AMONG PATIENTS WITH SCHIZOPHRENIA SWITCHED TO LURASIDONE FROM OTHER ANTIPSYCHOTICS**

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**Objective:** Patients with schizophrenia frequently switch between antipsychotics, underscoring the need to ensure that important treatment outcomes such as health-related quality of life (HRQL) are achieved and maintained following the switch. This analysis evaluated changes in overall health-related quality of life among patients with schizophrenia switched from current antipsychotic treatment to lurasidone.

**Methods:** Stable, but symptomatic outpatients with schizophrenia were switched from their current antipsychotic to lurasidone, in a 6-week, open-label trial, conducted in the US. The Personal Evaluation of Transitions in Treatment (PETiT) is a validated 30-item instrument measuring self-reported overall quality of life outcomes among patients with schizophrenia. In addition, PETiT assesses 2 domain scores on psychosocial functioning and adherence related attitude. Each item of PETiT is assigned a rating of 2, 1 or 0 where 2 denotes positive change and 0 denotes negative change. Higher scores on PETiT denote better HRQL. PETiT scale was administered at baseline and study endpoint. Changes from baseline to study endpoint in PETiT total score (overall HRQL) and domain scores (psychosocial functioning and adherence) were compared using ANCOVA with baseline score, treatment, and pooled site as covariates.

**Results:** Of the 244 patients switched to lurasidone from other antipsychotics, patients with available data on PETiT (n=213) were included in the analysis. Mean PETiT total scores at baseline was 35.3 and at study endpoint was 38.5. Mean change from baseline to the study endpoint in the PETiT total score was 3.2, change in psychosocial functioning domain score was 2.5, and change in adherence domain score was 0.7, significant in all patient groups (p<0.001).

**Conclusions:** The findings from this study indicate that patients switching from other antipsychotics to lurasidone experienced statistically significant improvement in HRQL, psychosocial functioning and adherence related attitude within 6 weeks of treatment. Further investigation regarding the effects of longer-term lurasidone treatment on HRQL outcomes is warranted.

**Learning Objectives:**

- At the conclusion of the presentation, participants will have a better understanding of the impact of switching antipsychotic medication in patients with a diagnosis of schizophrenia.
- At the conclusion of the presentation, participants will have a better understanding of the effect of short-term treatment with lurasidone on measures of health-related quality of life.

**Source of Funding:** This study was sponsored by Sunovion Pharmaceuticals Inc.

**Literature References:**

- Awad AG, Voruganti LN. Measuring quality of life in patients with schizophrenia: an update. *Pharmacoecon* 2012;30:183-95.
- Awad AG. Quality-of-life assessment in schizophrenia: the unfulfilled promise. *Expert Rev Pharmacoecon Outcomes Res.* 2011;11:491-3.

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## **NEUROCOGNITIVE FUNCTIONING AND AWARENESS OF ILLNESS IN SCHIZOPHRENIA: BASELINE CORRELATIONS AND LONG-TERM TREATMENT OUTCOMES**

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<sup>1</sup>University of Miami Miller School of Medicine, <sup>2</sup>Data Power Inc, <sup>3</sup>Sunivion Pharmaceuticals Inc.,

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**Objective:** The aim of this analysis was to evaluate the relationship between illness awareness and the ability to perform cognitive tests in a double-blind, controlled clinical study. The extent to which treatment-related improvement in awareness was related to improvement in cognition and functional capacity was also examined.

**Methods:** Patients with acute exacerbation of schizophrenia (N=488) were randomized to once-daily, fixed dose treatment with lurasidone 80 mg (LUR 80), lurasidone 160 mg (LUR 160), the active control quetiapine XR 600 mg (QXR) or placebo (PBO). Subjects who completed the initial 6-week trial were eligible to enroll in the double-blind extension study, involving continued treatment with flexible once-daily doses of lurasidone (40-160 mg; N=151) or QXR (200-800 mg; N=85). Subjects initially treated with PBO were started on flexible once daily doses of LUR (40-160 mg; N=56). Cognitive performance was examined with the CogState cognitive battery and functional capacity was assessed with the UPSA-B (up to week 32 of the extension study). Impairment of insight was assessed by PANSS item G12 “lack of judgment and insight” at baseline and at each of the post-randomization visits.

**Results:** Neurocognitive testing was performed on 481 patients. Of these, 214 patients (45%) failed the prespecified criteria for cognitive evaluation. The remaining 267 (55%) patients provided evaluable neurocognitive scores at both the baseline and week 6 assessments. Compared to the evaluable sample, we found the non-evaluable sample in the initial 6-week trial had a significantly higher proportion of acutely psychotic patients and a lower level of insight. PANSS Insight (G12) scores were significantly improved for LUR160, LUR80 and QXR groups compared to PBO after 6 weeks. Improved insight during the acute phase was a significant mediator for the effect of LUR160 (vs. placebo) on the neurocognitive composite score ( $p<0.05$ ), UPSA-B total score ( $p<0.05$ ), and the domain scores for verbal learning ( $p<0.05$ ) and social cognition ( $p<0.05$ ). Improvement in insight at week-32 was significantly greater in subjects treated with lurasidone compared with quetiapine XR. Improved insight during the double-blind extension phase was associated with better cognitive functioning and UPSA-B total change score ( $p<0.05$ ). Better insight at baseline predicted an increased likelihood for completion of cognitive testing and obtaining evaluable scores ( $p\leq 0.002$ ,  $N=481$ ).

**Conclusion:** Level of insight in patients with schizophrenia predicted the ability to validly complete cognitive assessments. Insight was significantly improved for the LUR160, LUR80 and QXR groups compared to placebo after 6 weeks. Improvement in insight at week-32 was significantly greater in subjects treated with lurasidone compared with quetiapine XR. Gain in insight predicted improvements in cognitive functioning and performance-based measures of functional capacity.

### **Learning Objectives:**

- To evaluate the impact of illness awareness on the ability to perform cognitive tests in a double-blind, controlled clinical study
- To learn interrelationships between illness awareness, cognitive performance and functional capacity.

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

### **Literature References:**

- Loebel A, Cucchiaro J, Sarma K, et al. 2013. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. *Schizophrenia Research*. 2013 (in press).
- Harvey P, Cucchiaro J, Pikalov A, Loebel A, Siu C. Cognitive performance in patients with schizophrenia treated with lurasidone: Results from a placebo- and active-controlled acute phase study followed by a 6 month double-blind extension. *Neuropsychopharmacology* 2011; 36: S134.

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## EFFECTS OF YOGA ON COGNITION AND EPIGENETIC CHANGES IN CHRONIC SCHIZOPHRENIC PATIENTS

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<sup>1</sup>NYU Medical School and Nathan Kline Institute for Psychiatric Research

**Introduction:** A few studies done in Asian countries have suggested that Yoga may be effective in improving cognition and psychiatric symptoms in schizophrenic patients.. Studies of response in glucocorticoid receptors in brain and blood have shown that behavioral treatments related to maternal care, maternal depression or stress and childhood abuse can alter glucocorticoid receptors and their epigenetic control. We present results from a study of the effects of Yoga on cognition and epigenetic and hormonal biochemical changes in chronic schizophrenic patients in the United States.

**Methods:** We conducted a study of Yoga in 36 chronic schizophrenic outpatients (schizophrenia or schizoaffective diagnosis) who participated in 12 weeks of Hatha Yoga (group 1) or later a modified Yoga concentrating more on Qigong movements and procedures (groups 2 and 3).. Subjects were evaluated at baseline and end for a) Cognition (RBANS), b) Psychiatric Symptoms (PANSS), and c) glucocorticoid receptor (GR), DNMT, and TET1 mRNA in lymphocytes. They were evaluated monthly for cortisol, and ACTH, TSH. They were also evaluated for weight and glucose-lipid responses.

**Results:** Three months of Yoga treatments produced significant *increases* in Cognitive Scores on RBANS Total Scores and Sum of Index Scores ( $P < .001$ ) and increases in most RBANS sub-scores of Attention Delayed Memory, Visual-Spatial, Language Index ( $P$ 's  $< .05$  -  $P < .001$ ). There were no significant changes in PANSS scores, although there was a trend for decrease on the Depression factor ( $P = .08$ ) and PANSS General Factor ( $P = .06$ ), and other scores showed a slight trend for decrease. There was a trend ( $P = .2$ ) for increase in serum ACTH and a tendency for increased cortisol. Serum cortisol and ACTH were highly correlated at baseline ( $r = .69$ ,  $P = .001$ ), but not correlated by 8 or 12 weeks of Yoga treatment ( $r$ 's =  $0.07$ -. $0.13$ ). 12 weeks of Yoga treatment significantly ( $P < .05$  -  $P < .01$ ) decreased in lymphocytes GR mRNA (by 30%), DNMT1 mRNA (by 23%) and TET1 mRNA (by 22%). There was a positive correlation of TET 1 mRNA levels with RBANS delayed memory index ( $r = .50$ ,  $P = .057$ ) and RBANS sum of index scores ( $r = .43$ ,  $P = .10$ ). There were positive correlations between baseline morning cortisol levels and RBANS scores (e.g. RBANS Total  $r = .47$ ,  $P = .036$ ). There were no significant changes in weight or glucose-lipid measures although waist circumference was slightly decreased ( $P < .01$ ).

**Conclusions:** Our results suggest that Yoga improves cognitive function in schizophrenic patients and may modify glucocorticoid receptor function and measures related to epigenetic regulation DNA methylation. Yoga may be an additional technique for improving cognition in schizophrenia. However, studies with appropriate controls, including exercise controls, are needed to further confirm or specify these effects.

### Learning Objectives:

- Participants will learn about effects of yoga on cognition in schizophrenia
- Participants will gain knowledge of effects of yoga on measure related to methylation of genes

**Source of Funding:** Private Philanthropic Grants

### Literature References:

- Bhatia T, Agarwal, Shah G, Wood J, Richard J, Gur R, et al (2012). Adjunctive cognitive remediation for schizophrenia using yoga: An open, non-randomized trial. *Acta Neuropsychiatrica* 24(91-100).

- Bhatia T, Agarwial, Shah G, Wood J, Richard J, Gur R, et al (2012). Adjunctive cognitive remediation for schizophrenia using yoga: An open, non-randomized trial. *Acta Neuropsychiatrica* 24(91-100).

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## **ASSESSING THE EFFECTIVENESS OF ARIPIPRAZOLE ONCE-MONTHLY VS. PALIPERIDONE PALMITATE FOR THE LONG-TERM TREATMENT OF SCHIZOPHRENIA**

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**Background:** The relative benefits of available antipsychotics in the long-term treatment of schizophrenia are mostly documented by indirect comparisons in the literature, and are often subject to controversy. Direct comparative studies assessing relative effectiveness reflecting real-life usage are preferred by European Health Technology Assessment agencies when assessing newly approved medicines. This is particularly true for studies with long-acting formulations aimed at addressing the comparative benefits of treatment in the long-term management of schizophrenia. Among the available and acknowledged endpoints to measure effectiveness, health-related quality of life is well established. This poster presents the overall study design of QUALIFY, a direct comparative study between aripiprazole once-monthly formulation and paliperidone palmitate, a long-acting formulation commonly used in the treatment of schizophrenia.

**Objectives and Methods:** The QUALIFY study is a 28-week, multi-national, randomized, open-label, rater-blinded, parallel-group, comparative effectiveness study comparing aripiprazole once-monthly with paliperidone palmitate on health-related quality of life, as measured by the Heinrichs–Carpenter Quality of Life Scale (QLS), in a close to real-life setting. Eligible patients will be aged 18–60 years, have a current diagnosis of schizophrenia (DSM-IV-TR criteria), and require chronic antipsychotic treatment. Patients will be stratified according to age, randomized, and converted from other antipsychotics to oral aripiprazole (10–30 mg/day) or paliperidone (3–12 mg/day), followed by a 6-month course of treatment with either aripiprazole once-monthly or paliperidone palmitate long-acting injectable formulations. The primary effectiveness endpoint is the QLS; additional assessments will include (among others) the Investigator’s Assessment Questionnaire, Clinical Global Impressions scales, and the Readiness to Work Questionnaire. Pharmaco-economic and safety assessments will also be performed.

**Results/implications:** Assessment of patient health-related quality of life, as well as other patient-relevant outcomes, allows for a more thorough assessment of comparative treatment effectiveness than traditional assessments of relapse or remission.

### **Learning Objectives:**

- To understand the value of using quality of life as an outcome measure to evaluate the effectiveness of treatments for schizophrenia
- To understand the design of a study evaluating the effectiveness of aripiprazole once-monthly versus paliperidone palmitate in adult patients with schizophrenia

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

### **Literature References:**

- Heinrichs et al. *Schizophr Bull* 1984;10:388–98
- Kazadi et al. *S Afr J Psychiatr* 2008;14:52–62

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## ADJUSTING ANTIPSYCHOTIC DOSAGE IN SCHIZOPHRENIA: GENOME-WIDE ANALYSIS OF CPZE EQUIVALENTS

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**Background:** In the recent years several studies have investigated genetic polymorphisms of antipsychotic drug metabolizing enzymes and receptors. However, most of the studies focused on drug response and very few have investigated the genetic influence on antipsychotic (AP) dosage. The aim of the present study is to test the association between AP dosage at genome-wide level.

**Methods:** The current dosage of AP medications was collected from 192 schizophrenic patients. The AP dosage was standardized using three different methods: CPZe according to Gardner et al. 2010, defined daily dose according to the WHO (2010) and percentage of maximum dose according to the Compendium of Pharmaceuticals and Specialties 2012 (Canada). The patients were then genotyped using the Illumina Omni 2.5 comprising of 2.3 millions SNPs. All markers were screened for nominal significance and for statistical significance after multiple-testing correction, using the FDR method.

**Results:** The preliminary analysis showed that the top SNP associated with CPZe was the rs1286769 on chromosome 3, however the significance did not survive the genome-wide correction.

**Discussion:** In this sample of 192 adults, the common variants investigated at genome-wide level had no major impact on the amount of antipsychotic medications that had been prescribed. However, studies combining large prescription databases and genome-wide data may identify genetic predictors to adjust the dose of antipsychotic medication.

### Learning Objectives:

- Know about different methods to standardize antipsychotic dosage
- Know about pharmacogenetic studies investigating antipsychotic dosage predictors

**Source of Funding:** Canadian Institute of Health Research: MOP-260282

### Literature References:

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## ONCE DAILY DOSING IMPROVES ASENAPINE EFFECTIVENESS, PATIENT ACCEPTANCE AND ADHERENCE AS COMPARED TO TWICE DAILY DOSING

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Asenapine is an oral second-generation antipsychotic that is administered sublingually. It has been released with FDA labeling for twice daily dosing of 5 to 10 mg bid. However, the terminal half-life of Asenapine is 24 hours and once daily dosing is likely to be effective in reducing psychopathology. In addition, once daily dosing is likely associated with improved patient acceptance relative to twice daily dosing. Therefore, we randomly assigned 24 patients, who had a psychotic exacerbation of schizophrenia or schizoaffective disorder, to up to 14 days of treatment with either Asenapine 5 mg BID or Asenapine 10 mg QHS. We compared the changes in their psychopathology after receiving treatment and also investigated the medication acceptance by patients in two groups. In once daily group, 22% patients discontinued the treatment before the end of the study, in contrast to 64% patients in twice daily group. The medication was discontinued due to intolerable side effect or inadequate therapeutic effect. Patient acceptance of the medication is rated as a scale of 1-7 with 1 as very acceptable and 7 as completely unacceptable. This scale is  $1.9 \pm 0.6$  (Mean  $\pm$  SE) in once daily group and  $4.0 \pm 0.6$  in twice daily group. Brief Psychiatric Rating Scale (BPRS) were measured at baseline, day 3, day 7 and day 14 after receiving treatment to evaluate psychopathology of patients. In once daily group, BPRS was reduced from  $41.1 \pm 2.47$  to  $25.3 \pm 2.21$  after Asenapine treatment. In twice daily group, BPRS was  $37.0 \pm 1.3$  at

baseline and  $30.2 \pm 2.6$  after treatment. In summary, our results indicate that Asenapine once daily dosing is associated with improved effectiveness, patient acceptance and adherence as compared to twice daily dosing. Further study is under investigation to determine whether this result could be applied to a larger patient population.

**Learning Objectives:**

- Investigate whether dosing change would affect the effectiveness of Asenapine treatment.
- Investigate whether dosing change would affect patient compliance of Asenapine treatment.

**Source of Funding:** This study is sponsored by Merck & Co., Inc.,

**Literature References:**

- S. Stoner, H. Pace. Asenapine: a clinical review of a second-generation antipsychotic. Clin Ther. 2012 May;34(5):1023-40
- S. Potkin. Asenapine: a clinical overview. J Clin Psychiatry. 2011;72 Suppl 1:14-8.

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**NEGATIVE AND POSITIVE SYMPTOM PROMINENCE, FUNCTIONING, QUALITY OF LIFE AND FAMILY BURDEN IN CATIE**

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**Background:** There is an increased interest to evaluate the impact of core symptoms of schizophrenia, both positive and negative, on functioning and burden of disease.

**Objective:** To examine the extent to which prominent positive and prominent negative symptoms impact functional health, well-being, health care related quality of life and family burden.

**Methods:** Data on symptomatology, quality of life and resource use from Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project were analyzed (n=1447). Patients were divided into four groups based on Positive and Negative Syndrome Scale using published criteria as having (a) *neither* prominent positive nor prominent negative symptoms (n=575; 40%); (b) only prominent *negative* symptoms (n=274; 18.9%), (c) only prominent *positive* symptoms (n=295; 20.4%) or (d) *both* prominent positive and negative symptoms (n=303; 20.9%) and group differences were examined for overall significance between the groups and for a linear trend.

**Results:** There was a significant linear decline with each subsequent group, with the combination of prominent positive and negative symptoms incrementing the decline further, on quality adjusted life years (QALYs) derived from the Short-Form-12, Index of functioning, derived from quality of life measures, PANSS derived QALY for schizophrenia and number of work days missed by caretaker during month prior to CATIE (all  $p < 0.001$ ).

**Conclusions:** Both prominent positive and prominent negative symptoms of schizophrenia are independently associated with significant decline in functional mental health, health related quality of life and caregiver lost days from work. An increased burden is observed in patients with highest symptomatology. Further research is needed to determine predictors of poor outcomes and burden of schizophrenia.

**Learning Objectives:**

- To learn how prominent positive and prominent negative symptoms impact functional health, well-being, health care related quality of life and family burden in schizophrenia.
- To learn how quality of life adjusted years can be computed for persons with schizophrenia using the Positive and Negative Syndrome Scale and SF-36.

**Source of Funding:** Supported by F. Hoffmann-La Roche Ltd.

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## ANTIDEPRESSANT EFFECTS ON CORTICAL THICKNESS IN MIDLIFE WOMEN WITH DEPRESSION

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**Objective:** Some women are at higher risk for Major Depressive Disorders (MDD) during midlife years. However, little is known about the impact of its treatment on the cerebral grey matter of this population. We examined the grey matter cortical thickness in midlife women with MDD before and after antidepressant treatment compared to healthy controls.

**Design:** Eighteen depressed, unmedicated women (mean age =  $50.1 \pm 4.6$  years; mean total MADRS scores =  $19.2 \pm 5.8$ ) and 23 healthy, age-matched controls ( $51.2 \pm 5.2$  years; MADRS scores =  $2.8 \pm 2.2$ ) underwent high-resolution structural MRI in a 3T scanner. After a 2-week placebo lead-in phase, non-responders received 8 weeks of SNRIs (Duloxetine 60-120 mg/day or Desvenlafaxine, 50 mg/day). MRI scanning was performed at baseline and after 8 weeks in both groups. The images were pre-processed to segment the brain and to align cortical structures using Freesurfer software. Voxel-wise cortical thickness maps were generated using depressive symptoms as covariates and age as a nuisance variable ( $p < 0.01$ ).

**Results:** Twelve patients and all healthy controls completed both scans. Baseline, analysis revealed cortical thinning in depressed subjects in the anterior cingulate cortex (ACC) and angular gyrus compared to controls. Depressed subjects presented thicker grey matter in the medial and lateral frontal cortex and superior temporal gyrus. Cortical thickness analysis using MADRS as covariate and correcting for age ( $N=41$ ) revealed that depressive scores were negatively correlated with grey matter thickness in the medial and lateral frontal cortex. After antidepressant treatment, (MADRS scores =  $5.9 \pm 5.8$ ,  $p < 0.05$ ), subjects showed increase in grey matter in ACC, superior frontal gyrus and temporal gyri. Healthy controls did not show changes compared to baseline scan.

**Conclusion:** This is a preliminary but quite novel study examining cortical thickness in MDD midlife women with diagnosis of depression before and after antidepressant treatment. These results suggest that the untreated depressive disorder in peri/postmenopausal women might have a negative impact in discrete brain regions. After 8 weeks, antidepressant treatment with SNRIs evoked changes in cortical thickness in brain areas associated with mood and cognitive control. Future studies should clarify the potential effects of pharmacologic treatments on cortical brain function in this vulnerable population.

### Learning Objectives:

- Unmedicated depression in midlife women might have an impact on the brain structure.
- Antidepressant treatment might evoked changes in cortical thickness in brain areas associated with mood and cognitive control.

**Source of Funding:** Father Sean O'Sullivan Research Award Program, St. Joseph's Healthcare Foundation, Hamilton, Ontario, Canada.

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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.

### Learning Objectives:

- Teachers will be aware of the contents of the 7th edition of the ASCP Model Psychopharmacology Curriculum for Training Directors and Teachers of Psychopharmacology in Psychiatric Residency Programs.
- Teachers will be aware of the contents of the 2nd edition of the ASCP Model Psychopharmacology Curriculum for Directors of Medical Student Education and Teachers of Psychopharmacology in Medical Student Programs.

**Source of Funding:** N/A

### Literature References:

- (2012). ASCP Model Psychopharmacology Curriculum for Training Directors and Teachers of Psychopharmacology in Psychiatric Residency Programs (7th ed.). Retrieved from <http://psychopharmacurriculum.com>
- (2013). ASCP Model Psychopharmacology Curriculum for Directors of Medical Student Education and Teachers of Psychopharmacology in Medical Student Programs. (2nd ed.). Retrieved from <http://psychopharmacurriculum.com>

## THE ROLE OF LONG ACTING INJECTABLE ANTIPSYCHOTICS IN FIRST EPISODE SCHIZOPHRENIA: A REVIEW OF EFFICACY AND TOLERABILITY

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The role of Long-acting antipsychotics in First Episode Schizophrenia; a review of efficacy  
U.C. Osuagwu(Osuchukwu), I. Jolayemi, D. Dada, K. Shah, K. Taher, C. Nnadi

**Introduction:** *Schizophrenia* is a clinical syndrome of chronic nature with variable, but profoundly disruptive, impact on the cognition, behavior, perception, and insight of affected individuals over the course of time. It is characterized by relapses alternating with periods of full or partial remission. The disorder usually begins insidiously before age 25, and becomes apparent when a clinically significant episode of psychosis occurs for the first time; (*First episode psychosis*) and persists throughout life. First episode schizophrenia increasingly has been recognized as a critical stage of the illness during which effective intervention may potentially change the long term outcome of the disease.

The role of Long Acting Injectable Antipsychotics (LAIA) have become notably encouraging in reducing the problem of non-adherence, reduce relapse and improve overall treatment outcome. There is cumulating evidence that LAIA may become the main stay of treatment in near future. However available data is limited on the efficacy and tolerability of LAIA in the treatment of first episode schizophrenia (FES).

**Method:** An extensive search for all articles and publications on the; effectiveness, time to remission, tolerability and attitude of patients and physicians toward use of LAIA in first episode schizophrenia was conducted using PubMed from 2000 to 2011.

**Results:** LAI have the potential to address the issues of poor compliance and all cause treatment discontinuation however there is still a risk of relapse even with LAIA. In one study the risk of re-hospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications. Time to relapse is variable but significantly longer in patient on LAIA.

**Conclusion:** Use of depot antipsychotics was associated with a significantly lower risk of re-hospitalization than use of oral formulations of the same compounds. In unstable chronic schizophrenics LAIA may not be superior to oral antipsychotic as only a minority of patients adheres to their injections and the majority does not stay long enough on LAIA to sustain their benefits.

**Learning Objectives:**

- To determine the degree of efficacy of long acting injectable forms of antipsychotic medication in the overall management of first episode psychosis
- To explore the myth or the facts in the acceptability and tolerability of injectable Long acting medications in patients with first episode psychosis

**Source of Funding:** Weiden PJ. Maintenance treatment with long-acting injectable risperidone in first-episode schizophrenia: a randomized effectiveness study. The journal of clinical psychiatry. 2012-09-01;73:1224-33.

**Literature References:**

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**RISK BENEFIT & DECISION ANALYSES OF ELECTRO-CONVULSIVE THERAPY (ECT) IN MAJOR DEPRESSION, MANIA & SCHIZOPHRENIA**

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**Purpose/Content:** Non-response to medications is becoming an increasing concern: the NIMH sponsored STAR\*D trial (Trivedi et al, 2006) showed that in a community sample, only one-third of patients will achieve remission from an antidepressant trial, and up to one-third will not achieve remission after four different treatment trials. Our research goal is to develop a decision model for ECT use in treatment refractory depressed patients with a diagnosis of depression or bipolar disorder. Medications are first-line treatment for depressive episodes in major as well as bipolar depression. The objective of this research project is to develop a risk-benefit analysis and decision model for ECT use in depressed patients. The analysis and model will assist rational decision making to balance benefits and adverse events of ECT in psychiatric patients with a specific profile of disease characteristics and individual values. Use of this treatment option and related decision tool will help maximize the benefits in accordance to individual patient values. This project is developing a new scientific and technical tool, namely an evidence-based model for clinical decision making, to make the application of ECT less burdensome, more efficient and more patient-centered.

**Methods:** In order to develop a new decision model deployable for a patient-centered evaluation of ECT utilization in treatment-refractory depressed patients, our risk-benefit analysis as well as decision model are going to be based on probabilities of beneficial and adverse effects of ECT captured by a systematic literature review and meta-analysis.

A literature review was conducted in NCBI's PubMed using the following search syntax:

- (("electroconvulsive"[All Fields] OR "convulsive therapy"[mesh] OR "electroshock"[mesh] OR "ECT"[All Fields] OR "electroshock"[All Fields] OR "convulsive"[All Fields]) AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp])) AND English[lang])

The actual process of decision model building is carried out by use of the TreeAge® software.

**Results:** A systematic literature review was done using the search syntax outlined above. The search yielded a total of 3072 titles. Using the limitation parameters from the methods section, 2846 articles were excluded. The review of 226 randomized clinical trials comparing different ECT modalities or ECT vs. sham ECT/placebo, no ECT or antidepressants led to the structure of the decision analysis tree (displayed on the poster) and will inform the probabilities to be associated with each branch of the tree.

Probabilities are currently added to each branch of the decision analysis tree, based on pooled evidence from published randomized trials about the effectiveness and safety of ECT. In addition, focus groups with clinicians, experts, patients and patient's relatives will assist in imputing a range of plausible values for each outcome (effectiveness and safety) into the decision model of ECT for treatment refractory depression.

#### **Learning Objectives:**

- Learning Objective 1: To develop an understanding of an evidence-based risk-benefit decision analysis model of ECT vs. other interventions that can assist clinical decision making for the treatment of refractory depression.
- Learning Objective 2: To develop an understanding of an evidence-based risk-benefit decision analysis model of different modalities of ECT that can assist clinical decision making for the treatment of refractory depression.

#### **Source of Funding:**

FDA/CDRH Critical Path Project, FY 2010: "Risk Benefit & Decision Analysis of Electro Convulsive Therapy (ECT) in Major Depression, Mania & Schizophrenia." P.I.: Dr. Federico Soldani

#### **Literature References:**

- The Efficacy of Acute Electroconvulsive Therapy in Atypical Depression. Hussain et al. Mar 2008, J Clinical Psych
- NIMH sponsored STAR\*D trial (Trivedi et al, 2006)

## KETAMINE IN TREATMENT RESISTANT DEPRESSION: WHAT IS THE CURRENT EVIDENCE?

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**Background:** The role of monoamine neurotransmitters (serotonin, nor-epinephrine, dopamine) in pathophysiology of depression is well documented, but evidence regarding the role of glutamate system is still not clear. Many treatment options (TCA, SSRI, SNRI, ECT, augmentation strategies) are available in market for treatment resistant depression, but currently available drugs have delayed onset of action. Ketamine, a NMDA- glutamate receptor antagonist has shown some promise as a novel antidepressant with its rapid onset of action.

**Objective:** Our objective was to systemically review the literature to summarize the current evidence for the use of ketamine in treatment resistant depression including its effect on suicidality, relapse of depressive symptoms and adverse events associated with ketamine.

**Search Strategy:** Systemic electronic search of the literature was conducted. Published English language manuscripts were considered for review. A comprehensive search of electronic databases e.g. PubMed, PsychInfo, OvidMedline and the Cochrane library using broad terms was completed. We also searched the references list of relevant articles.

**Selection Criteria:** We focused only on the human studies between 2000 to 2012. We selected randomized controlled trials and open label investigations using ketamine for the diagnosis of major depressive disorder (treatment-resistant depression) not responding to  $\geq 2$  antidepressants. All participants must be physically healthy without any medical comorbidities and substance abuse. Case series and case reports were excluded. We excluded studies using ketamine for bipolar depression.

**Data collection:** We assessed quality of each article with separate tools as appropriate by study design. Two reviewers independently assessed quality for each study and extracted the data. Final decision was made by rating on quality assessment tool and consensus of the team.

**Results:** From a total of 176 articles, 7 articles (6 open label investigations and 1 controlled trial) were identified. Six studies used single dose ketamine infusion and noticed significant improvement in depressive symptoms over time as evidenced by score change in rating scales such as MADRS, BDI, and HDRS. Only one study used repeated ketamine infusion (6 infusions) and found similar results. Most of the participants in these studies relapsed between 7 days to 45 days. Although main focus of the results in these studies was overall score in rating scales, two studies found significant change in suicidality item score. While ketamine was well tolerated in all 7 studies, significant adverse effects included dissociation, dizziness, headache, elevations in blood pressure, perceptual disturbances and resolved in first 24 hours.

**Conclusion:** There is a scarcity of randomized, double blind, controlled trials for the use of ketamine as anti-depressant. Current evidence suggests that ketamine can induce rapid improvement in depression and can be seen as a novel anti-depressant in future as it can revitalize the traditional anti-depressant therapy. Given significant adverse events associated with the use of ketamine, more clinical trials are required to determine whether ketamine can be successfully considered in TRD.

### Learning Objectives:

- Our objective was to systemically review the literature to summarize the current evidence for the use of ketamine in treatment resistant depression.
- To review the evidence of ketamine's efficacy in reducing suicidal ideation and relapse of depressive symptoms

**Source of Funding:** Ketamine for treatment-resistant unipolar depression: current evidence. Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N, Ostermeyer B, Murrough JW. CNS Drugs. 2012 Mar 1;26(3):189-204. doi: 10.2165/11599770-000000000-00000. Review. PMID: 22303887 [PubMed - indexed for MEDLINE]

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### CAN WE TRUST PROS AS RELIABLE MEASURES OF SEVERITY OR CLINICAL CHANGE?

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We speak of a patient reported outcome as if it was *one* reliable outcome on one subject, for one constant time frame, for one symptom, collected at one moment in time. This may be an oversimplification. There may be multiple possible reasonable PROs for this one subject - one time frame - one phenomenon. The presenter will show data illustrating this complex from a recent dataset. This raises some problems in trying to assess PRO validity and therefore the accurate measurement of severity and change over time. Since many PROs need some patient education/instruction/training on accurate completion of a PRO, inadequate or inconsistent instructions and expectations can affect the PRO result. The metric used, whether Likert scale, visual analog scale or DISCAN scale can influence the sensitivity of the scale. The method used to collect the data, whether using paper and pencil, IVRS, electronic data capture (edc), whether surveillance of the data acquisition, the use of or immediate presence of an informant or family member/significant other or consequences for certain scores can affect the validity of the data. Patient ratings when left alone are often more revealing and yield more severe scores than the clinician ratings on the same day. Clinicians appear to rate more improvement than the patient over the same time frame. But there are some notable exceptions. Cynics may argue that since a clinician rated scale has 2 levels of distortion, first the patients distortion and then the clinicians in the final rating, it would be better to rely on the PRO rather than the CRO, since you can adjust for one level of distortion better than for 2. Not enough time, effort and care are given in PRO scale development and to Delphi method with individual patients, to focus groups and to cognitive debriefing. Critical phenomena may be misunderstood and included in scales leading to structural distortion within the scale and these distortions yield misleading results. A novice patient's sense of symptom change over time may differ from the perception of the experienced clinician who sees many patients with the same illness every day. All these issues will be illustrated with concrete examples from psychiatry research studies. Awareness of and use thoughtful methods and strategies to address these limitations can enhance reliability of PROs and improve accuracy in measuring severity and change over time.

### Learning Objectives:

- Appreciate the limitations of the reliability of PROs in measuring severity and change in psychiatric research.

### Literature References:

- Appreciate the methodology and strategies that have evolved to enhance reliability of PROs in psychiatric research and how data in PROs can enhance and complement the information collected in clinical measures