NCDEU
New Research Approaches for Mental Health Interventions

# NCDEU 52nd Annual Meeting Poster Abstract Book

## *Identifying Common Targets Across Brain Diseases – Implications for Treatment Development and Delivery*

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## Arizona Biltmore Resort & Spa
## Phoenix, Arizonaa

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POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## THE ALPHA7 NEURONAL NICOTINIC RECEPTOR (NNR) MODULATOR TC-5619 SHOWED EFFICACY SIGNALS AND WAS GENERALLY WELL TOLERATED IN A PHASE 2 TRIAL IN ADULTS WITH ATTENTION-DEFICIT / HYPERACTIVITY DISORDER (ADHD)

David Hosford, MD, PhD[1], Paul Newhouse, MD[2], Alexandra Potter, PhD[3], Geoffrey Dunbar, MD[4], Jessica Beaver, PhD[4], Anthony Segreti, PhD[4]

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NNR agonists may help symptoms of ADHD [1,2]. TC-5619 is a selective alpha7 NNR modulator with efficacy in preclinical models of memory [3]and was generally well tolerated in phase 1 trials in healthy volunteers, demonstrating a robust improvement in attention at 6.8mg in a multiple rising dose study. The present trial was conducted to test the effect of TC-5619 in adults with ADHD.

The study randomized 135 male or female adults (ages 18 – 65 years) with ADHD from sites in the US, diagnosed per DSM-IV-TR criteria. Subjects were randomized to 12 weeks of treatment using either placebo (n = 67) or TC-5619 (n = 68: 1mg po qd for 4weeks, then 5mg po qd for 4 weeks, and finally 25mg po qd for 4 weeks).

TC-5619 did not separate from placebo on the primary outcome measure (Conners Adult ADHD Rating Scale – Investigator [CAARS-Inv] total score) at Weeks 4, 8 or 12 and, consequently the study did not meet predefined success criteria. However, the CAARS-Inv did show a statistically significant result favoring TC-5619 at Week 1 ($p = 0.019$). All p-values reported are one sided. The study included a variety of secondary outcome measures, including the CAARS-Inv subscales, the CAARS subject-rated (CAARS-S) subscales, the CogState ADHD Test Battery (CATB), Clinical Global Impression – Improvement (CGI-I) and CGI-Severity (CGI-S) and Profile of Mood States (POMS). The results favored TC-5619 with statistical significance ($p < 0.05$) sporadically at at least one time point on: CAARS-Inv Hyperactivity-Impulsivity scale; all CAARS-S subscales (ADHD Index, Hyperactivity, Inattentive and Problems with Self-Concept); some CATB tests (Stop Signal Reaction Time, a test of behavioral inhibition; Groton Maze Learning Test (GMLT); Detection task, a test of psychomotor processing; and the International Shopping List Task, a test of verbal learning); CGI-I and CGI-S; and behavioral items in the POMS for anger-hostility and confusion-bewilderment.

In a post hoc analysis of subpopulations by ADHD subtype, subjects with the inattentive type (n = 30) not only drove those results that favored TC-5619 in the total population, but also showed a statistically significant benefit on CAARS-Inv total score at Weeks 1 ($p = 0.005$) and 4 ($p = 0.027$), as well as on a number of CAARS-Inv and CAARS-S item scores.

TC-5619 was generally well tolerated, with no clinically significant change in any safety measure.

Although TC-5619 did not separate from placebo on the primary outcome measure at Weeks 4, 8 or 12, positive signals of the compound's effects were observed in a variety of CAARS-Inv and CAARS-S scales, CATB items, CGI-S, CGI-I, and POMS items. Moreover, a post hoc analysis in the results for subjects with the predominantly inattentive type of ADHD favored TC-5619 with statistical significance on CAARS-Inv total score, as well as a variety of other outcome measures. Together, these results indicate that TC-5619 has promise as a treatment for adults with ADHD.

**Learning Objectives:**

- Properties of alpha7 modulator, TC-5619
- Potential efficacy of nicotinic agonists for ADHD
- Efficacy of TC-5619 in predominantly inattentive ADHD
- Safety and tolerability of TC-5619 in individuals with ADHD

**Source Of Funding:** Targacept, Inc.

**Literature References:**

- Levin ED, Conners CK, Sparrow E, Hinton SC, Erhardt D, Meck WH, Rose JE, March J: Nicotine effects on adults with ADHD. Psychopharmacology 1996; 123: 55-63.
- Potter AS, Newhouse PA: Effects of acute nicotine on behavioral inhibition in adolescents with ADHD. Psychopharmacology 2004; 176: 182-194.
- Hauser TA, Kucinski A, Jordan KG, Gatto GJ, Wersinger SR, Hesse RA, Stachowiak MK, Papke RL, Lippiello PM, Bencherif M: TC-5619: An á7 NNR selective agonist that demonstrates efficacy in animal models of the positive and negative symptoms and cognitive dysfunction in schizophrenia. Biochemical Pharmacology 2009; 78: 803-812.

## RELIABILITY AND RELIABLE CHANGE OF THE CAARS SELF-REPORT SHORT VERSION (CAARS-S:S) AND OBSERVER SCREENING VERSION (CAARS-O:SV) SCALES IN ADULT ADHD

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**Introduction**: Test-retest reliability and the reliable change indices (RCI) are important sources of information for ongoing data monitoring and assessing change associated with treatment. Although published data on the CAARS suggests adequate test-retest reliability additional data is needed in the context of clinical trials. We evaluated the short-term test-retest reliability and reliable change indices of the CAARS self and observer reports in a US based adult ADHD study.

**Materials and Methods**: Data were obtained from 133 subjects for the CAARS-S:S and O:SV (Conners et al., 1999) upon screening and baseline as part of a 12 week, phase 2 study of placebo versus verum. The sample consisted of 78 men and 55 women with an average age of 38 (SD = 13). Average time between assessments was 17 days (SD=5.6 days). Descriptive statistics, Pearson correlation coefficients, paired-samples t-tests, and RCI calculations (Jacobson and Truax, 1991) were used to evaluate scale reliability and change.

**Results and Discussion**: Current test-retest reliability values (correlation coefficients) for the S:S ranged from .75 for the inattention subscale to .84 for the hyperactive scale (with a median of .82 across the 5 subscales; whereas the CAARS-O:SV exhibited a tighter range (.79 to .80 among the 4 subscales) with no notable differences among subscales. Paired samples t-tests revealed small but statistically significant decreases in both self and investigator ratings across the relatively short screening period (22.37 to 21.71 $p<.05$ for the S:S ADHD Index; and 22.17 to 21.62 $p<.05$ for the O:SV ADHD Index). These changes should be interpreted in the context of the reliable change scores analyses which suggest RCIs for the S:S and O:SV ADHD Index scores of 6 (95% CI); and should help inform the planning and interpretation of adult ADHD trials.

**Learning Objectives:**

- Review test-retest reliability for ADHD outcome scales used in clinical trials
- Review application of RCI to ADHD scales in clinical trials

**Source Of Funding:** Worldwide Clinical Trials

**Literature References:**

- Conners, C.K., Erdhart, D., Sparrow, E. (1999). CAARS Adult Rating Scales Technical Manual. Multi-Health Systems, NY.
- Jacobson, N.S. & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. Journal of Consulting and Clinical Psychology, 59, 12-19.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## ROLE OF PATIENT CHARACTERISTICS AND RESEARCH DESIGN FEATURES IN CLINICAL TRIAL OUTCOME OF FDA APPROVED MEDICATIONS FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A REVIEW OF PUBLICATION BIAS FREE DATA FOR 3,843 PATIENTS

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**Background:** In the past twenty five years, twelve new medications have been approved for use with ADHD among children, adolescents and adults in the US. Interestingly, the initial reliance on amphetamines has somewhat shifted as three non-amphetamine agents have been approved in the past decade. In this context, it is unclear if factors such as the age of ADHD patients, severity of illness, duration of a clinical trials and type of pharmacological agent have any role to play in the outcome of ADHD trials, a phenomenon seen in other psychiatric illnesses (1,2).

**Methods:** We reviewed 12 New Drug Applications including 7 supplemental applications from the FDA that included 39 randomized, placebo controlled Phase II-IIIB clinical trials for ADHD. Of these, 16 trials with 3,843 patients met our inclusion criteria for analysis including a parallel design model and investigator rated scale derived from DSM-IV criteria for ADHD.

First, we evaluated if there were differences in the magnitude of placebo response, medication-placebo differences among the three groups of ADHD patients based on age (children, adolescents and adults).

Next we evaluated if factors such as severity of ADHD symptoms at randomization, odds of receiving active treatment, duration of ADHD trial, percentage of males in each of the trials, and type of ADHD medication (amphetamines versus non-amphetamine) had any relationship to the ADHD trial outcome using a multi-factorial linear regression model.

**Results:** There were 2,512 (937 children, 494 adolescents, and 831 adults) patients assigned to an investigational medication and 1,331 (444 children, 199 adolescents, and 522 adults) to placebo.

The magnitude of symptom reduction with placebo was similar among children and adults (about 20%) whereas it was significantly higher among adolescents (about 32%, $p<0.01$). However, the medication-placebo difference as measured by effect sizes was 0.91 in children, whereas it was 0.42 among both adults and adolescents. Although none of the ADHD trials failed, the subgroup analysis for the adolescents among three trials failed.

Surprisingly, the relationship between baseline severity of ADHD symptoms and medication-placebo differences were large ($r$=0.7). This strong relationship minimized any other significant relationship to the drug-placebo differences among the factors evaluated.

**Conclusions:** These data suggest that ADHD trial outcomes follow a pattern seen among other psychiatric illnesses such as depression and bipolar mood disorder. Specifically, medication-placebo differences are related to age of the patients. Also, baseline severity of symptoms may play a role in the outcome of ADHD trials. It is interesting to note that ADHD symptoms may respond to more than one class of medications, a phenomenon common in most psychiatric illnesses.

**Learning Objectives:**

- To evaluate if research design features may influence apparent efficacy of ADHD medications by influencing medication-placebo difference scores.
- To assess if patient characteristics inclusive of age and sex influence ADHD medication-placebo difference scores.

**Source Of Funding:** None

**Literature References:**

- Tarr G et al. Study design and patient characteristics and outcome in acute mania clinical trials. Bipolar Disord 2011;13:125-32.
- Khan A et al. Research design features and patient characteristics associated with outcome of antidepressant clinical trials. Am J Psychiatry 2004;161:2045-9.

## DEVELOPMENT AND PHARMACOKINETIC CHARACTERIZATION OF DELAYED, PULSATILE-RELEASE ONDANSETRON FORMULATION

J. Corey Fowler, PhD[1], Steven T. Szabo, MD, PhD[2], Ashwin Patkar, MD[2], Barry Magnum, PharmD[3], Wayne F. Beyer, PhD[4], Lan-Yan Yang, PhD[4], Shein-Chung Chow, PhD[4], Bruce K. Burnett, PhD[5], Brett Froeliger, PhD[2], Tong H. Lee, MD, PhD[2]

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Psychostimulant abuse generates profound socioeconomic, legal and medical problems worldwide, and is a significant comorbid factor that can adversely affect the clinical courses of other psychiatric disorders. While several agents, all employed as monotherapies, have failed to show consistent clinical efficacy against psychostimulant dependence, previous preclinical studies have demonstrated that combinations of a dopamine (DA) agonist (~~p~~sycho-stimulant substitute") and a 5-$HT_3$ antagonist can reverse behavioral and neurobiological alterations in animal models of psychostimulant abuse. Additional consideration of these results have also indicated that the 5-$HT_3$ antagonist plasma concentration need to peak ($C_{max}$) a few hours after oral administration. To that end, we have developed two different approaches for pulsatile-release of ondansetron (Ond-PR). Preclinical in vitro dissolution kinetics of our pulsatile-release ondansetron formulations have proven effective and Phase 1 studies are presented herein. One of the tested formulations provided an optimal $C_{max}$ separation following simultaneous oral administration with methylphenidate (MPh); no untoward drug-drug interactions were observed. We are currently conducting a Phase II study to test efficacy of MPh + Ond-PR specific combination treatment in abstinent psychostimulant abusers.

**Learning Objectives:**

- Novel Treatment Strategies for Substance Abuse
- Neural Mechanisms Underlying Craving to Drugs of Abuse

**Source Of Funding:** NIDA sponsored GO Grant: NCT01377662

**Literature References:**

- Kamal S. Bhatia, Steven T. Szabo, J. Corey Fowler, William C. Wetsel, Tong H. Lee. "Reversal of long-term methamphetamine sensitization by combination of pergolide with ondansetron or ketanserin, but not mirtazapine: Preclinical Insight towards Novel Treatment Strategies in Stimulant Abuse." Behav Brain Res. 2011 Sep 30;223(1):227-32.
- Davidson C, Gopalan R, Ahn C, Chen Q, Mannelli P, Patkar AA, Weese GD, Lee TH, Ellinwood EH. Reduction in methamphetamine induced sensitization and reinstatement after combined pergolide plus ondansetron treatment during withdrawal. Eur J Pharmacol. 2007 Jun 22;565(1-3):113-8.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## 5-HTT AND DRD4 GENETIC POLYMORPHISMS AND FAMILY HISTORY AS MODERATORS OF BACLOFEN'S EFFECTS ON DRINKING AND EFFECTS OF ALCOHOL: A PRELIMINARY DOUBLE-BLIND CONTROLLED RANDOMIZED HUMAN LABORATORY STUDY

Lorenzo Leggio, MD, PhD, MS[1], George A. Kenna, PhD, PharmD[1], William H. Zywiak, PhD[2], John E. McGeary, PhD[1], Steven Edwards, BS[1], Samuel R. Fricchione, BS[1], Tonya Tavares, BS[1], Jessica R. Shoaff, BS[1], Christine Goodwin, MS[1], Eugenia Gurvich[1], Robert M. Swift, MD, PhD[1]

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**Background:** Prior preclinical and clinical studies have identified the GABAB receptor agonist baclofen as a possible pharmacotherapy for alcohol dependence (AD). Some studies, however, have generated conflicting results, highlighting the need for identifying subtypes of patients who may be the best responders to baclofen treatment.

**Methods:** We conducted a human laboratory study to investigate putative biobehavioral mechanisms by which baclofen reduces drinking. This was a between-subject double-blind controlled randomized pilot trial. We enrolled 14 non-treatment seeking alcohol dependent (AD) participants who received baclofen 10mg t.i.d. or an ‗active' placebo (i.e. cyproheptadine 2mg t.i.d.) for 8 days. Then, participants came to our lab to perform a session consisting of an alcohol cue-reactivity (CR) experiment, followed by an alcohol self-administration (ASA) experiment. Measurements of craving [Alcohol Use Questionnaire (AUQ)], attention [Alcohol Attention Scale (AAS)], salivation, sedation and stimulation [Biphasic Alcohol Effects Scale (BAES)] were performed. Polymorphisms in the D4 dopamine receptor (DRD4) gene and in the 5-HTTLPR promoter region of the serotonin re-uptake transporter (5-HTT), severity of AD (determined by number of current DSM-IV AD criteria, and Alcohol Dependence Scale [ADS] score), family history (FH) of alcoholism, and early vs. late-onset alcoholism were explored as potential moderators of baclofen's effects.

**Results:** 13 out of the 14 subjects (Ss) completed the laboratory session. For both stimulation and sedation, we found a significant increase in the baclofen group compared to placebo. DRD4 status moderated medication effects on both sedation and stimulation, and FH status moderated medication effects on stimulation. In particular, sedation scores were greatest for those Ss receiving medication with a 7 or greater repeats in the DRD4 gene (519 base pairs or greater), and lowest for those receiving placebo with a 7 or greater repeats in the DRD4 gene. Also, sedation scores were greatest for those Ss with a subtype LL on the 5-HTT gene who received medication; and the lowest for those Ss with a subtype LL who received placebo. Finally, during the ASA experiment, there was a reduction in alcohol self-administration in the baclofen group compared to active placebo.

**Conclusions:** It's been suggested that baclofen reduces alcohol drinking by reducing the individual's craving for alcohol. This study shows that the reduction in drinking might be secondary to the stimulation and sedation effects from baclofen. Interestingly, sedation was ‗controlled' for by using an ‗active' placebo that induces sedation. Furthermore, previous treatment clinical trials with baclofen have provided conflicting results, and this study, albeit preliminary, provides evidence of potential endophenotypes who might respond best to baclofen treatment.

**Learning Objectives:**

- Baclofen has a pharmacological treatment for alcohol dependence
- Effects of baclofen on the biphasic effects of alcohol can be moderated by genetic polymorphisms and family history of alcoholism

**Source Of Funding:** Brown University Center for Alcohol and Addiction Studies

**Literature References:**

- Leggio L, et al. Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. CNS Neurol Disord Drug Targets. 2010;9:33-44.
- Addolorato G, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007;370:1915-22.
- Edwards S, et al. Current and promising pharmacotherapies, and novel research target areas in the treatment of alcohol dependence: a review. Curr Pharm Des. 2011;17:1323-32.

## NOP AGONISM: A NOVEL MECHANISM FOR THE TREATMENT OF ANXIETY AND DEPRESSION

Carla M. Canuso, MD, James Hutchison, PhD, Prasarn Manitpisitkul, PhD, John A. Moyer, PhD

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JNJ-XXXX is a novel, centrally active, potent and selective, nociceptin/orphanin-FQ peptide (NOP) receptor agonist. It has shown anxiolytic and antidepressant activity in numerous animal models. Several of these studies suggest an inverted U-shaped dose-response curve. 5 clinical studies evaluated the safety/tolerability (S/T), pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple oral doses in healthy adults. This presentation reviews results from 2 studies, with emphasis on PD effects.

Study 1: Randomized, DB, pbo-controlled, single-dose study exploring effects of JNJ-XXXX on rCMglu using [18F] FDG PET, and assessing the S/T and PK of single oral doses of 50mg and 125mg in healthy males. While neither the 50mg nor 125mg dose showed statistically significant changes in mean rCMglu in the hypothalamus, amygdala, or hippocampus compared to pbo, consistency was observed with regard to regions of effect between Day 1 vs Day -1 and Day 2 vs Day -1 in the 50mg group, but not in the pbo or 125mg groups. There appeared to be an inverted U-shaped dose-response curve for glucose metabolism in the hypothalamus based on statistical parametric mapping analyses, as the effect was observed in the 50mg group but not the pbo or 125mg groups.

Study 2: A two-part, DB, pbo-controlled single (part 1) and multiple (part 2) dose study evaluating effects of JNJ-XXXX on CCK-4 induced anxiety, S/T and PK in healthy males. Part 1 had 2 cohorts; one randomized subjects to 50mg (n=12) or pbo (n=6) and the other randomized subjects to 125mg (n=12) or pbo (n=6). In part 2 36 subjects were randomized to 50mg, 125mg or pbo. In part 1 CCK-4 50 µg iv was given the day following the dose of JNJ-XXXX, and after 7 days of treatment in part 2. Anxiety was measured before and after CCK-4 dosing with the Spielberger State Anxiety Inventory (SSAI) and Total Panic Symptom Score (TPSS), respectively. In part 1, no differences were seen on SSAI for either dose cohort vs pbo. The LS mean (SE) difference on TPSS in 50mg cohort vs pbo was -3.7 (2.9) (at alpha=0.1, one-sided level, p=0.1097); in the 125mg cohort LS mean difference was 5.2 (3.4), favoring pbo. In part 2, SSAI was also significantly lower (p=0.0565) in the 50mg group vs pbo, but not in the 125mg group. There was no difference between both treatment groups and pbo on TPSS.

PK and S/T results were consistent across both studies. All subjects receiving JNJ-XXXX showed systemic exposure, with median $t_{max}$ occurring at 1-6 hrs. Steady state was not achieved in either study. Most AEs were mild; GI-related effects were reported most commonly (up to 38%).

PD results from these two studies suggesting an inverted U-shaped are consistent with preclinical data, and inform dosing for future trials of JNJ-19385899 to further understand the utility of NOP agonism in the treatment of anxiety and depression.

**Learning Objectives:**

- Demonstration of PD studies informing dosing
- Explore potential of NOP agonist in the treatment of anxiety and depression

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## TRIGEMINAL NERVE STIMULATION IN POST-TRAUMATIC STRESS DISORDER AND MAJOR DEPRESSION: A NOVEL NEUROMODULATION APPROACH

Ian A. Cook, MD[1,2], Christopher M. DeGiorgio, MD[3], Andrew F. Leuchter, MD[2]

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**Objective:** Modulation of brain activity via stimulation of the Trigeminal Nerve (TNS) is an emerging therapy for epilepsy, with an excellent safety profile and significant reductions in seizures in pilot studies in subjects with medically refractory epilepsy [1]. The Trigeminal nerve has reciprocal projections to the nucleus tractus solitarius, the locus coeruleus, and the reticular formation, suggesting TNS may be able to alter activity in structures implicated in mood regulation and anxiety disorders [2]. In this proof-of-concept project, the effects of TNS were examined in Post-traumatic Stress Disorder (PTSD) with comorbid unipolar Major Depressive Disorder (MDD) as an adjunct to pharmacotherapy. We present findings on the first six evaluable subjects.

**Methods:** Six adults (mean age 54.3 (s.d. 14.1) years, 4F:2M) with median 28 yrs since traumatic exposure (range 10-56)) and with PTSD and MDD, were studied in an 8-week open label outpatient trial at an academic medical center. Current episodes were required to be of at least 4 mo. duration, with non-response to at least 1 antidepressant trial over at least 6 weeks during the current episode (ATHF $\geq$ 1), and concomitant use of at least 1 antidepressant. All had prominent symptoms at entry, with mean scores on the PTSD Patient Check List (PCL) of 60.8 (s.d. 6.9) and on the Quick Inventory of Depressive Symptoms (QIDS-C) of 16.0 (4.7). Subjects placed stimulating electrodes over the supraorbital branches of the trigeminal nerve for at least 8 hours per day (primarily while asleep), with current adjusted to maximal comfortable levels. Co-primary outcomes were change in PCL and QIDS-C at 8 weeks.

**Results:** TNS was well tolerated. Decreases in PCL score were significant, from 60.8 (6.9) at entry to 32.5 (18.5) at week 8 (2-tail paired t-test p=0.03). QIDS-C score decreases were also significant, falling from 16.0 (4.7) at entry to 5.5 (4.8) at week 8 (p=0.02). Both reflect a large effect size comparing end-of-trial to start (Cohen's *d* 1.8 for PCL and 2.2 for QIDS-C).

**Conclusions:** Significant decreases in PTSD and depression severity were achieved in the 8 weeks of acute TNS treatment. This novel approach to brain stimulation may have use as an adjunct to pharmacotherapy in these disorders. Additional examinations will be needed to delineate efficacy and tolerability with greater reliability, and to examine the range of therapeutic parameters (~~-d~~ose finding").

**Learning Objectives:**

- To describe changes in symptoms of PTSD associated with 8-weeks of trigeminal nerve stimulation
- To describe changes in symptoms of major depression associated with 8-weeks of trigeminal nerve stimulation

**Source Of Funding:** Miller Endowed Chair, intramural UCLA funds, and an investigator-initiated research grant from NeuroSigma

**Literature References:**

- DeGiorgio CM. "Trigeminal Nerve Stimulation: Seminal Animal and Human Studies for Epilepsy and Depression." Neurosurgical Clin N Amer. 2011. 22(4):449-56.
- Schrader LM. "Trigeminal Nerve Stimulation in Major Depressive Disorder: First Proof of Concept in an Open Pilot Trial." Epilepsy Behav. 2011. 22(3):475-8.

## MIXED DEPRESSION: A STUDY OF ITS PHENOMENOLOGY AND RELATION TO TREATMENT RESPONSE

Prakash Masand, MD[1], Chi-Un Pae, MD, PhD[2], Paul A. Vöhringer, MD, MS[3], Niki S. Holtzman, BS[4], Sairah B. Thommi, BS[3], William Gilmer, MD[5], Ashwin Patkar, MD[6], S. Nassir Ghaemi, MD, MS[4]

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**Methods:** In 72 patients treated in a randomized clinical trial (ziprasidone versus placebo), we assessed the phenomenology of manic symptom type at study entry and their influence as predictors of treatment response.

**Results:** The most common symptom presentation was a clinical triad of flight of ideas (60%), distractibility (58%), and irritable mood (55%). Irritable mood was the major predictor of treatment response. DSM-based diagnostic distinctions between MDD and bipolar disorder (type II) did not predict treatment response.

**Conclusion:** In this prospective study, mixed depression seems to be most commonly associated with irritable mood, flight of ideas, and distractibility, with irritability being an important predictor of treatment outcome with neuroleptic agents. If these data are correct, in the presence of mixed depression, the DSM-based dichotomy between MDD and bipolar disorder does not appear to influence treatment response.

**Learning Objectives:**

- To be familiar with symptoms associated with mixed depression
- To identify symptomatic predictors of antipsychotic response in mixed depression

**Source Of Funding:** Pfizer

**Literature References:**

- Patkar A,et al. A 6 week randomized double blind placebo controlled trial of Ziprasidone for the acute depressive mixed state.Plos One In press.
- Benazzi F Which could be a clinically useful definition of depressive mixed state? Prog.Neuropsychopharm Biol Psych.2002;26:1105-1111.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## THE EFFICACY OF MEMANTINE FOR COGNITIVE DEFICITS IN EUTHYMIC SUBJECTS WITH BIPOLAR DISORDER

Dan V. Iosifescu, MD[1,2], William S. Gilmer, MD[3], Alexander Fan, MD[4], Atilla Gonenc, PhD[5], Constance Moore, PhD[6], Christopher Randolph, PhD[7], Mark H. Rapaport, MD[8], Thilo Deckersbach, PhD[2], Andrew A. Nierenberg, MD[2]

[1]Mount Sinai School of Medicine, New York, NY, [2]Massachusetts General Hospital, Boston, MA, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]McLean Hospital, Belmont, MA, [6]University of Massachusetts Medical School, Worcester, MA, [7]Loyola University Medical Center, Chicago, IL, [8]Emory University School of Medicine, Atlanta, GA

**Background:** Subjects with bipolar disorder experience significant cognitive dysfunction, even when euthymic, but few studies have evaluated potential treatments for such deficits.

**Method:** We randomized 72 euthymic subjects with bipolar disorder, who reported subjective cognitive deficits. Subjects were assigned flexible doses (5-20 mg/day) of memantine or placebo (using a ratio 2:1 respectively) for a 12-week treatment study. At baseline and endpoint all subjects were administered neuropsychological tests, including tests of attention (the Rapid Visual Information Processing Task, RVIP of CANTAB), short-term/working memory (the Spatial Working Memory, SWM of the CANTAB), verbal and episodic memory (the California Verbal Learning Test, CVLT-II and the Delayed Matching to Sample, DMS of the CANTAB). We also administered the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which includes five subscales (attention, immediate memory, visuospatial construction skills, delayed memory and language). Mood scales and subjective cognitive questionnaires were administered monthly. We collected proton magnetic resonance spectroscopy (1H-MRS) data from a subset of patients before and after treatment. MRS data was acquired from two 15x15x15 mm voxels centered on left and right hippocampus. Study completers were offered open label treatment with memantine for additional 12 weeks; neuropsychological tests were again administered at the end of the follow-up.

**Results:** Over 12 weeks, the memantine group showed significant improvements over placebo in spatial and working memory (SWM: Between errors, Strategy, Total Errors), verbal and episodic memory (DMS: Percent correct and Total correct; CVLT: Trial 2 ; Trial 4; Recognition hits; Recognition of false positives), total RBANS score and three of five RBANS indexes (attention, language and delayed memory). Compared to placebo (N=3), memantine-treated subjects (N=6) had increases in left hippocampus NAA, a measure of neuronal viability, and in the right hippocampus choline (Cho). The initial improvements in neuropsychological tests during randomized treatment were maintained over 12 weeks of open follow-up.

**Conclusion:** Memantine was associated with acute improvements on several cognitive domains in euthymic bipolar subjects over 12 weeks and such improvements persisted with ongoing treatment for an additional three months. Memantine was also associated with MRS measures of increased hippocampus neuronal viability.

**Learning Objectives:**

- Understand the importance of cognitive deficits for the functional disability in bipolar disorder
- Discuss the potential efficacy of memantine as a potential treatment for cognitive dysfunction in bipolar patients

**Source Of Funding:** Supported by Forest Laboratories (grants to Drs. Nierenberg, Iosifescu, Gilmer and Rapaport)

**Literature References:**

- Malhi GS, et al. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. Bipolar Disord 2007; 9:114–125.
- Iosifescu DV, et al. Galantamine-ER for cognitive dysfunction in bipolar disorder and correlation with hippocampal neuronal viability: a proof-of-concept study. CNS Neurosci Ther. 2009; 15(4):309-19.

## URIDINE ALTERS FRONTAL LOBE PHOSPHOLIPID METABOLISM AND REDUCES DEPRESSIVE SYMPTOMS IN ADOLESCENT BIPOLAR DEPRESSION: A PHOSPHORUS-31 MAGNETIC RESONANCE SPECTROSCOPY STUDY

Douglas G. Kondo, MD, Kristen K. Fiedler, BS, Tracy L. Hellem, BS, Xianfeng Shi, PhD, Young-Hoon Sung, MD, Rebekah S. Huber, MS, Perry F. Renshaw, MD, PhD

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**Objective:** The neurobiology of juvenile BD is poorly understood, and novel treatments are urgently needed. The pyrimidine compound uridine has been studied in adult BD. Human and animal studies show that uridine impacts brain phospholipid synthesis. Pyrimidines also improve catecholamine synthesis and mitochondrial function. To investigate the neurochemistry of adolescent BD, we performed Phosphorus-31 magnetic resonance spectroscopy (31P-MRS) brain scans before, and after, open treatment with uridine, in depressed adolescents with BD, and a group of healthy controls (HC).

**Method:** Study inclusion criteria were: age 13-18 with bipolar type I, II or NOS as determined by the K-SADS-PL; current depressive episode lasting >2 weeks, and CDRS-R score >40. Participants received fixed-dose uridine 500mg BID for 6 weeks. 31P-MRS scans at 3 Tesla were used to measure pre- and post-treatment frontal lobe metabolites relevant to mitochondrial function and phospholipid metabolism. HC underwent identical brain scans.

**Results:** 24 BD adolescents and 24 HC were enrolled. Baseline 31P-MRS scans were obtained on (N=14) bipolar adolescents, and post-treatment scans were acquired on (N=12) of these participants. At baseline, adolescents with BD showed alterations in phosphocreatine (PCr; p=0.03) and inorganic phosphate (Pi; p=0.01) compared with HC. Post-hoc Tukey-Kramer analysis showed that un-medicated BD had decreased Pi compared with both HC (17%; p=0.03), and medicated BD participants (22%; p=0.02).

BD adolescents' mean CDRS-R score decreased from 57.5 to 32.8 (p=0.0001; Cohen's d Effect Size=2.2). Repeated measures 31P-MRS neuroimaging showed that uridine was associated with increased glycerophosphoethanolamine (GPE) of 85.83% (p=0.005), and decreased glycerophosphocholine (GPC) of 31.44% (p=0.03). The lower GPE levels at baseline may indicate reduced membrane turnover, resulting from impaired energy metabolism. Uridine was well-tolerated and there were no SAEs, suicide attempts or hospitalizations.

**Conclusions:** Our results support the view that frontal lobe mitochondrial function is altered in adolescent BD, and may have implications for the use of Pi as a biomarker. Consistent with preclinical studies, BD participants demonstrated significant changes in frontal lobe phospholipid metabolism--most notably a sharp rise in GPE. Elevated GPE may signal increased membrane synthesis, because phospholipid levels remain constant, with degradation balancing synthesis. Furthermore, the compound phosphatidylethanolamine (PE) accounts for up to 45% of the brain's lipid content, with the highest levels found in mitochondria. When PE synthesis is accelerated, the excess phospholipid is degraded to GPE. Further translational study of uridine as a treatment for depressed adolescents with BD is warranted.

**Learning Objectives:**

- To become familiar with utilization of magnetic resonance spectroscopy to study pediatric mood disorders
- To be able to discuss magnetic resonance spectroscopy neuroimaging biomarkers in adolescent bipolar depression
- To acquire knowledge of a hypothesis-driven nutritional supplement treatment for depressed adolescents with bipolar disorder

**Source Of Funding:** NARSAD

**Literature References:**

- Chang K: Challenges in the diagnosis and treatment of pediatric bipolar depression. Dialogues Clin Neurosci 2009; 11:73–80.
- Agarwal N, Sung YH, Jensen JE, daCunha G, Harper D, Olson D, Renshaw PF: Short-term administration of uridine increases brain membrane phospholipid precursors in healthy adults: a 31-phosphorus magnetic resonance spectroscopy study at 4T. Bipolar Disord 2010; 12:825-33.
- Yoon SJ, Lyoo IK, Haws C, Kim TS, Cohen BM and Renshaw PF: Decreased glutamate/glutamine levels may mediate cytidine's efficacy in treating bipolar depression: a longitudinal proton magnetic resonance spectroscopy study. Neuropsychopharmacology 2009; 34:1810-1818.
- Hattingen E, Magerkurth J, Pilatus U, Mozer A, Seifried C, Steinmetz H, Zanella F, Hilker R: Phosphorus and proton magnetic resonance spectroscopy demonstrates mitochondrial dysfunction in early and advanced Parkinson's disease. Brain 2009; 132(Pt 12):3285-97.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## CARIPRAZINE IN THE TREATMENT OF ACUTE MANIA IN BIPOLAR DISORDER: A DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III TRIAL

Anjana Bose, PhD[1], Anju Starace, BS[1], Qing Wang, PhD[1], Elizabeth Diaz, MD[1], Jennifer Goodman, BS[1], Adam Ruth, PhD[2], György Németh, MD, PhD[3], István Laszlovszky, PhD, PharmD[3]

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**Objective:** Cariprazine, a $D_3$-preferring dopamine $D_3/D_2$ receptor partial agonist, is a novel antipsychotic in development for the treatment of schizophrenia and bipolar mania. Higher affinity for and greater receptor antagonism at $D_3$ versus $D_2$ receptors, may be associated with antipsychotic efficacy, better tolerability, and beneficial effects on mood. A Phase III clinical trial (NCT01058096) evaluated the efficacy, safety, and tolerability of cariprazine in patients with acute mania associated with bipolar I disorder.

**Methods:** In a 6-week, multicenter, placebo-controlled, parallel-group, flexible-dose study, patients (age, 18-65 years) with acute mania associated with DSM-IV-TR–defined bipolar I disorder and a Young Mania Rating Scale (YMRS) score ≥20 were randomized to cariprazine 3-12 mg/day or placebo for 3 weeks of double-blind treatment. Patients were hospitalized for a 4-7 day wash-out screening and at least 14 days of treatment. There was a subsequent 2-week safety follow-up period. Primary efficacy endpoint: YMRS total score change from baseline to the end of Week 3 analyzed using a mixed-effects model of repeated measures (MMRM) approach on the intent-to-treat (ITT) population; secondary efficacy: Clinical Global Impressions-Severity (CGI-S). Safety was evaluated by adverse events (AEs), clinical laboratory values, vital signs, electrocardiograms (ECGs), and extrapyramidal symptom (EPS) scales.

**Results:** A total of 312 patients were randomized and received at least 1 dose of double-blind treatment (placebo, 154; cariprazine, 158); 69% and 68% of placebo and cariprazine patients, respectively, completed the study. Baseline YMRS scores were similar between groups (placebo, 32.0; cariprazine, 32.8). Statistically significant improvement was demonstrated in cariprazine 3-12 mg/day patients relative to placebo on YMRS (LSMD, -4.3; $P<.001$; MMRM) and CGI-S (LSMD, -0.4; $P<.01$; MMRM) change from baseline to Week 3. Overall premature discontinuation rates were similar for cariprazine and placebo patients (32% and 31%); 10% of cariprazine- and 7% of placebo-treated patients discontinued due to AEs.. Treatment-emergent AEs (TEAEs) occurred in 80% and 63% of cariprazine and placebo patients, respectively; the most common AEs (≥10% and twice the rate of placebo) were akathisia, extrapyramidal disorder, tremor, dyspepsia, and vomiting. EPS-related AEs occurred in 46% and 12% of cariprazine and placebo patients, respectively.

**Conclusions:** Results from this Phase III study demonstrated that cariprazine was effective in the treatment of acute mania associated with bipolar I disorder. Cariprazine was safe and generally well tolerated in this group of patients.

**Learning Objectives:**

- At the conclusion of this session, the participant should be able to discuss the efficacy of cariprazine in the treatment of acute mania associated with bipolar I disorder.
- At the conclusion of this session, participants should be able to evaluate the tolerability profile of cariprazine in the treatment of bipolar acute mania.

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

**Literature References:**

- Kiss B: 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.
- Gyertyán I: Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. Neurochem Int. 2011;59(6):925-35.

## CARBAMAZEPINE MONOTHERAPY MANINTENANACE TREATMENT

Seville Gamer, MD[1], Eric D. Peselow, MD[1]

[1]RUMSC, Staten Island, NY

**Introduction:** Bipolar disorder is a chronic illness with alternating periods of remissions and relapses (manic or hypomanic stage, depression, or mixed stage. One of the major aspects of Bipolar Disorder treatment is that maintenance therapy which could prevent relapses and increase the length of remission. Many research studies were conducted to evaluate efficacy of each known mood stabilizer: Lithium, Divalproex acid, Carbamazepine in the maintenance phase of bipolar illness. This paper presents a naturalistic study of Carbamazepine monotherapy in the maintenance treatment of bipolar illness.

**Method:** The patients involved in this naturalistic study were treated in one of two NYC outpatient clinic over a 20 year period. Patients signed informed consent to allow the collection of clinical data. The patients' age range was from 18 to 80 years. 71 patients were evaluated over an average 35 months (from 2 months to 108months). These patients had been diagnosed Bipolar I Disorder on Axis I, with the diagnosis being made using the SCID scale..These patients were started on Carbamazepine in acute stage and adjunct was done by either anxiolytic, or antidepressant, or antypsychotic medications. All adjunct medications were weaned off as soon as patient was stabilized. The patients were stable for 6 months before prophlaxis was considered to be begun. Patients were then followed until they either terminated well (remained well until Jan 1, 2010 theendpoint of our evaluation), dropped out of treatment or relapsed wth a manic/hypomanic or depressive episode

**Results:** Of the 71 patients, 32 remained continuously well (13 for greater than 5 years, and 19 for from 2 months to 5 years) 25 relapsed (15 with a depressive episode and 10 with a hypomanic/manic episode) and 14 droppped out. The average probability of remaining well on carbamazepine maintenance was 83 % at 1 year, 56% at 3 years and 40% at 5 years.

**Conclusion:** Despite adequate prophylactic treatment many of patients relapsed. The study will be discussed and compared with the double-blind studies of carbamazepine maintenance.

**Learning Objectives:**

- To understand the need for long-term treatment in bipolar illness
- To evaluate the efficacy of carbamazepine in bipolar illness

**Source Of Funding:** None

**Literature References:**

- Chou JCY. Review and Update of the APA Practice Guideline for Bipolar Disorder. Primary Psychiatry 2004; 11(9):73-84.
- Nasrallah HA, Ketter TA et al. Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. J Affect Disord. 2006; 95(1-3):69-78.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## SIX-MONTH OUTCOMES OF CUSTOMIZED ADHERENCE ENHANCEMENT (CAE) THERAPY IN BIPOLAR DISORDER

Martha Sajatovic, MD[1], Jennifer Levin, PhD[2], Curtis Tatsuoka, PhD[3], Weronika Micula-Gondek, MD[4], Edna Fuentes-Casiano, LSW[2], Christopher S. Bialko[2], Kristin A. Cassidy[2]

[1]Department of Psychiatry and Neurological Outcomes Center, Case Western Reserve University, Cleveland, OH, [2]Department of Psychiatry, Case Western Reserve University, Cleveland, OH, [3]Neurological Outcomes Center, Case Western Reserve University, Cleveland, OH, [4]Georgetown University Hospital/Washington Hospital Center, Washington, DC

**Background:** This was a 6-month prospective trial of a psychosocial intervention (customized adherence enhancement/CAE) among 43 medication non-adherent individuals with bipolar disorder (BD) who were receiving treatment in a community mental health clinic (CMHC).

**Methods:** CAE was flexibly administered in modules applied as indicated by an initial adherence vulnerabilities screening. Screening identified reasons for non-adherence and modules were then administered using pre-set criteria. CAE effects were evaluated at 6 week, 3-month and 6-month follow-up. Primary outcome was change from baseline in adherence using the Tablets Routine Questionnaire (TRQ) and pill counts. Secondary outcomes included change from baseline in BD symptoms (Hamilton Depression Rating Scale (HAM-D), Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS).

**Results:** Subjects completed 86% of scheduled sessions with only 2 individuals (5%) not participating in any sessions. Dropout at 6-months was 12 (28%). Mean baseline non-adherence by TRQ was 48% (standard error (SE) 4.8%) missed tablets within the past week, and 51% (4.1%) missed tablets within the past month. At 6-month follow-up, mean TRQ non-adherence improved to 25% (6.8%) for the past week (p=.002), and 21% (5.5%) for the past month (p<.001). Symptoms improved with change in baseline mean BPRS of 43.6 (1.8) vs. endpoint of 36.1 (2.3; p=.001), and baseline mean HAMD of 17.8 (1.1) vs. endpoint of 15.3 (1.6; p=.044).

**Conclusion:** CAE was well-accepted by sub-optimally adherent CMHC bipolar patients, and was associated with improvements in adherence, symptoms, and functional status. Controlled trials are needed to confirm these preliminary findings.

**Learning Objectives:**

- Participants will gain greater understanding of reasons why individuals with bipolar disorder may not adhere to prescribed pharmacotherapies
- Participants will gain greater understandinig of behavioral interventions that might improve adherence with prescribed pharmacotherapies among patients with bipolar disorder

**Source Of Funding:** Grant from the NIMH (R34MH078967)

**Literature References:**

- Velligan D, et al. Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness. The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness. Journal of Clinical Psychiatry 2009; 70(4 Suppl): 1-48.
- Sajatovic M, et al. Enhancement of treatment adherence among patients with bipolar disorder. Psychiatric Services 2004; 55: 264-269.

## RELATIONSHIP OF CHANGE IN ADIPOSITY TO PSYCHIATRIC SYMPTOM CHANGE DURING RANDOMIZED INITIAL ANTIPSYCHOTIC TREATMENT IN PEDIATRIC DISRUPTIVE BEHAVIOR DISORDERS

Ginger E. Nicol, MD[1], Michael D. Yingling, BS[1], Karen S. Flavin[1], Julia A. Schweiger[1], John W. Newcomer, MD[2]

[1]Washington University School of Medicine, St. Louis, MO, [2]Miller School of Medicine, University of Miami, FL

**Background:** A positive predictive relationship between weight gain and therapeutic efficacy during antipsychotic treatment has been reported in schizophrenic adults, (1) despite well-known adverse health effects associated with weight gain in this population. (2) The relationship between weight gain and treatment response in youth treated with antipsychotic agents for disruptive and/or aggressive behaviors has not been evaluated.

**Methods:** Hypotheses regarding changes in body composition predicting therapeutic response to antipsychotic were tested using data from the MEAC study (Metabolic Effects of Antipsychotics in Children, MH72912, PI Newcomer). Antipsychotic naïve children ages 6-18 (N = 144) presenting with disruptive behavior in the setting of one or more DSM IV diagnoses were randomized to 12 weeks of treatment with olanzapine, risperidone, or aripiprazole, with pooled treatment group changes analyzed. Body composition was evaluated using Dual Energy X-Ray Absorptiometry (DEXA), Body Mass Index (BMI), BMI percentile and BMI z-score. Psychiatric symptoms were measured using the Aberrant Behavior Checklist (ABC) irritability, hyperactivity and total scores.

**Results:** Changes in ABC irritability subscale and ABC total scores significantly predicted changes in BMI percentile ($F[1,126]=10.448$, $p=0.002$; $F[1,126]=11.509$, $p=0.001$), BMI z-score ($F[1,126]=8.203$, $p=0.005$; $F[1,126]=9.218$, $p=0.003$), DEXA % body fat ($F[1,126]=4.276$, $p=0.041$; $F[1,126]=4.765$, $p=0.31$) and DEXA % lean mass ($F[1,126]=4.353$, $p=0.039$; $F[1,126]=4.804$, $p=0.030$). BMI%ile ($F[1,126]=6.586$, $p=0.011$) and BMI z-score ($F[1,126]=4.998$, $p=0.027$) also significantly predicted change in ABC hyperactivity scores. However, the amount of variance explained was small and directionality of effects indicated a tendency for symptoms to worsen with increasing adiposity.

**Discussion:** These results are relevant to the evaluation of potential risks and benefits during treatment with antipsychotic medications in youth treated with antipsychotics. The results indicate that commonly occurring increases in adiposity during initial antipsychotic treatment are not associated with clinical improvement, with a tendency for poorer treatment outcomes in relation to greater increases in adiposity.

**Learning Objectives:**

- Understand methods used to evaluate changes in body composition during antipsychotic treatment.
- Understand the relationship between changes in adiposity and therapeutic response during antipsychotic treatment for disruptive behavior.

**Source Of Funding:** MH72912, P30DK056341, UL1RR024992

**Literature References:**

- Meltzer HY, Perry E, Jayathilake K. Clozapine-induced weight gain predicts improvement in psychopathology. Schizophr Res. 2003;59(1):19-27.
- Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. Jama. 2007;298(15):1794-6.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## THE LITHIUM ARCHIVES PROJECT: THE ROLE OF LITHIUM IN THE PROTECTION OF NEURODEGENERATIVE AND CARDIOVASCULAR DISEASE

Ronald R. Fieve, MD[1,2], Monica L. Gilbert[2], Barbara Orlowski, PhD[3], Michael Oliva[4]

[1]Columbia University, New York, NY, [2]Foundation for Mood Disorders, New York, NY, [3]New York Medical College, New York, NY, [4]New York University, New York, NY

**Background**: Since the 1950's Lithium has been used worldwide in the successful treatment of bipolar disorder and there is consensus over the last 5 decades in the literature that for this illness it remains the most researched and effective treatment yet discovered. Despite the extensive literature on Lithium and Bipolar illness, there is a surprising dearth of literature investigating any potential relationship between lithium and neurodegenerative or cardiovascular disease. The following represents a summary of the new and recent literature regarding lithium's prophylactic properties in neurodegenerative and cardiovascular disease: Advancements in neuroscience suggest that Lithium increases gray matter volume and therefore may also have neuro-protective properties against diseases such as stroke, Alzheimer's and Parkinsonism. In addition to its widely studied neuro-protective properties, lithium has also been shown to have a low incidence of suicide attempts when compared to other medications used to treat bipolar disorders, such as valproate, but little exists in the literature showing any relationship between lithium and cardiovascular disease. The Lithium Archives Project is based on systematic chart reviews of over 8,000 patients with mood disorders treated at the New York State Psychiatric Institute's Lithium Clinic (NYSPI) and two affiliate lithium clinics of Columbia University (CUMC) and the Foundation for Depression and Manic Depression, which is now known as the Foundation for Mood Disorders (FMD), over the past 40 years. This is a retrospective naturalistic study which includes over 100 variables that can be analyzed collectively or autonomously.

**Methods**: The research design used in the Lithium Archives Project is a retrospective, random electronically scanned patient medical chart review conducted by a trained research scientist. The charts of patients with mood disorders are examined for over 100 variables including neurological and cardiovascular diseases, eye disorders, medication history, a wide range of side effects, demographics and patient and family histories. The current sample size of over 800 charts was analyzed by a skilled statistician using standard SPSS statistical software. Mean, standard deviation and significance of cerebrovascular disease, myocardial infarction, brain tumors, stroke, and seizures of patients treated with lithium and patients treated without lithium were compared and analyzed. Multivariate analysis was performed to analyze group (lithium/no lithium) and incidence of disease. The means of disease incidence in the lithium versus non-lithium groups were then charted.

**Results**: The Multivariate Analysis of Variance of the current data shows that group (patients treated with lithium versus those not treated with lithium) is a significant variable in the incidence of diseases analyzed (Pillai's Trace F = 2.926, df = 11,416, p=.004). The patients treated with lithium show less incidence of myocardial infarction ($p$=.014), seizures ($p$=.091, stroke ($p$=.014) and brain tumors ($p$=.072).

**Discussion:** The current analysis is very promising and indicates that in this patient population, lithium may indeed have played a role in protection from developing both cardiovascular and neurodegenerative diseases. There is not enough data to analyze for Alzheimer's or Parkinsonism. The entry of data into the Lithium Archives Project is an ongoing team effort, therefore results and number of diseases that can be analyzed may change as the database increases. As this database grows, further studies will be carried out to compare treatment outcomes, family history, demographics, comorbidity of neurological, cardiovascular and other medical diseases, medication history, and side effects of patients with mood disorders.

**Learning Objectives:**

- Increase awareness of prophylactic properties of Lithium
- Possible additional treatment of and protection from medical diseases

**Source Of Funding:** Private donations

**Literature References:**

- Fieve, R. R. (1999). Lithium therapy at the millennium: a revolutionary drug used for 50 years faces competing options and possible demise. Journal of Bipolar Disorders, 1, 67-70.
- Moore, JG, et al. A longitudinal study of the effects of lithium treatment on prefrontal and subgenual prefrontal gray matter volume in treatment-responsive bipolar disorder patients. J of Clinical Psychiatry. 2001; 70(5):699-705.
- Goodwin, F, et al. (2003;290(11)). Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA , 1467-1473.

## NORADRENERGIC CONTRIBUTORS TO AGGRESSION AND SELF-INJURY IN AUTISM SPECTRUM DISORDERS: ATOMOXETINE TREATMENT OUTCOMES IN A CASE SERIES

Jessica A. Hellings, MD, Irfan Bhatti, MD, Shumaila Younas, MD

Kansas University Medical Center, Kansas City, KS

**Background:** Aggression and self-injurious behavior (SIB) are common challenging behaviors which often respond only partially to antipsychotic treatment in individuals of all ages with Autism Spectrum Disorders (ASD). While risperidone (RIS) and aripiprazole (ARI) are FDA-approved to treat these problems in individuals aged 6 years and older, we hypothesize that the NE reuptake pump inhibitor atomoxetine (ATN) may improve partial antipsychotic response by targeting impulsivity.

**Method:** We reviewed 20 consecutive charts of patients meeting DSM-IV-TR criteria for ASD, who received ATN treatment for aggression and/or SIB. Data points extracted were: age, gender, ASD type, Intellectual Disability (ID) level, presentation of aggression, SIB or impulsivity, ATN dose, ATN duration, Clinical Global Impressions (CGI)-Severity at baseline, CGI-Improvement rated at each follow-up visit, and number of the follow-up visits. Also, extracted were AEs, and concomitant medications.

**Results:** Thirteen were male and 7 female; 15 had Autistic Disorder; 5 had PDDNOS. Mean age was 17.6 years (range 5-50). One individual was gifted; other intellectual disability (ID) levels were: 3 mild, 1 severe; 2 profound; 13 unspecified but with severe disability clinically. Nineteen subjects were aggressive; 12 manifested SIB; 20 were impulsive. Mean ATN treatment duration was 66.0 weeks (range 3-386); mean ATN dose was 0.7 mg/kg/day (0.4-1.2). Mean CGI-S at baseline was 5.4; mean percentage of follow-up visits with CGI-I improvement of ¡Ü 2 (Much Improved or Very Much Improved) was 71.8% (range 0-100). Behavioral worsening occurred in 3 subjects (15%), headache resulted in discontinuation in 1, tachycardia occurred in 5 (25%), appetite decrease in 1. Concomitant medications were RIS: 11 subjects; paliperidone:1; ARI:3; ARI plus RIS:1. Seven received antiseizure medications, breakthrough seizures occurred in 1 subject.

**Conclusions:** ATN doses were generally lower (mean 0.7 mg/kg/day) than recommended for the general population. A high rate of response occurred in individuals of all ages including those with severe ID with ATN together with RIS or ARI. Prospective combination studies are warranted.

**Learning Objectives:**

- To appreciate possible benefits of ATN in aggression and SIB in individuals with ASD and even severe ID.
- To encourage combination studies of ATN and RIS or ARI.

**Source Of Funding:** None

**Literature References:**

- Hellings JA; Zarcone JR; Reese RM; Valdovinos MG; Marquis JG; Fleming KK; Schroeder SR: A crossover study of risperidone in children, adolescents and adults with mental retardation. J Autism Dev Disord 2011; 36:401-411.
- Tamminga CA: When is polypharmacy an advantage? Am J Psychiatry 2011; 168:663.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## DEPRESSION IN MILD DEMENTIA: PRELIMINARY OUTCOMES OF A PILOT INTERVENTION

Michelle M. Hilgeman, BS, PhD[1,2]

[1]Tuscaloosa VA Medical Center, Tuscaloosa, AL, [2]Tuscaloosa Research Education and Advancement Corporation (TREAC), Tuscaloosa, AL

**Background:** Over half of individuals with dementia will suffer from clinically significant depressive symptoms during the course of the disease placing them at an increased risk for institutionalization and mortality.[1] However, research on the prevalence of comorbid depression in dementia has indicated that those receiving antidepressants do not consistently report less symptoms than those who are untreated pharmacologically.[2]

**Purpose of the study:** We examined a brief manualized psychosocial intervention entitled, Preserving Identity and Planning for Advance Care (PIPAC), which targets coping and quality of life in individuals in the early stages of dementia.

**Design and Methods:** Blocked randomization stratified by race and gender was used to assign participants and a family member to either the: (a) multi-component intervention group, or the (b) minimal support phone contact control group. Of the 19 dyads randomly assigned, 18 completed post-treatment assessment (i.e., 10 intervention and 8 control). Individuals with dementia were M = 82.8 (SD = 6.46) years old; six (31.6%) were men and 13 were women (68.4%). Participants were predominantly Caucasian (94.7%) with one African American (5.3%) individual with dementia. Family contacts were M = 70.14 (*SD* = 12.16) years old and were predominantly spouses (47.4%) or adult children (42.1%). They were 84.2% Caucasian and 12.5% African American.

**Results:** ANCOVAs controlling for baseline revealed clinically meaningful differences (i.e., medium to large effect sizes) between groups at post-treatment for self-reported depressive symptoms (F=5.50, d=1.25) and proxy-reported depressive symptoms (F=1.72, d=0.64). Anxiety indicators on the Cornell Scale for Depression in Dementia did not reveal differences between groups. However, health-related quality of life indicators were also promising (e.g., reduced mobility dependence F=272, d=.82).

**Implications:** The PIPAC intervention shows promise as a brief, manualized, psychosocial treatment for individuals in the early stages of dementia. Feasibility data demonstrated successful implementation, acceptability, and practicality of the intervention package. Planning for a future efficacy trial is underway.

**Learning Objectives:**

- After attending this activity, participants will be able to identify potential behavioral strategies to improve depression symptoms in mild dementia.
- After attending this activity, participants will be aware of a new manualized treatment approach in development for individuals with mild dementia.

**Source Of Funding:** Center Mental Health & Aging, University of Alabama Summer Research Fellowship

**Literature References:**

- Verkaik R, et al.: The relationship between severity of Alzheimer's Disease and prevalence of comorbid depressive symptoms and depression: a systematic review. Int J Geriatr Psychiatr 2007; 22, 1063-1086.
- Verkaik R, et al.: Comorbid depression in dementia on psychogeriatric nursing home wards: which symptoms are prominent? Am J Geriatr Psychiatr 2009;17(7), 565-573.

## MERCK NEUROSCIENCE PHARMACEUTICAL PIPELINE: JUNE 2012

David Michelson, MD[1], Armin Szegedi, MD, PhD[2]

[1]Merck & Company, North Wales, PA, [2]Merck Research Laboratories, Rahway, NJ

Merck is focused on several disease areas within neuroscience, and two molecules of interest currently in clinical development are MK-8931, a BACE inhibitor being studied as a potential treatment for Alzheimer's Disease, and MK-4305, an orexin receptor being studied for insomnia. A body of new data has provided information about these novel mechanisms, and about their potential value as therapeutics, which will be discussed in this 10 minute presentation.

**Learning Objectives:**

- Attendees will learn about a novel intervention in the amyloid pathway being investigated for Alzheimer's disease.
- Attendees will learn about the potential of orexin receptor antagonism as a treatment for insomnia.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## THE EFFECT OF DESVENLAFAXINE 50 MG/D ON A SUBPOPULATION OF ANXIOUS/DEPRESSED PATIENTS: A POOLED ANALYSIS OF 7 RANDOMIZED, PLACEBO-CONTROLLED STUDIES

Susan G. Kornstein, MD[1], Christine J. Guico-Pabia, MD[2], Rana S. Fayyad, PhD[3]

[1]Virginia Commonwealth University School of Medicine, Richmond, VA, [2]Pfizer, Inc., Collegeville, PA, [3]Pfizer, Inc., New York, NY

**Background**: The efficacy of desvenlafaxine (DVS) 50 mg/d compared with placebo for treating patients with MDD and concurrent anxiety symptoms was assessed in a post hoc pooled analysis.

**Methods**: Data were pooled from 7 double-blind, fixed-dose studies in adult patients with a diagnosis of MDD based on DSM-IV or DSM-IV -TR. Patients were randomly assigned to DVS or placebo. A subpopulation of these patients were identified with a baseline score ≥7 on the HAM-$D_{17}$ Anxiety-Somatization (A/S) factor. Primary end point was improvement in HAM-$D_{17}$ scores from baseline at week 8 (last observation carried forward [LOCF]) in the subpopulation of patients with a baseline score ≥7 on the HAM-$D_{17}$ Anxiety-Somatization (A/S) factor). Secondary outcomes included response (≥50% reduction in HAM-$D_{17}$) and remission (HAM-$D_{17}$ ≤7) rates; CGI-I and CGI-S scale scores, and improvement in MADRS and SDS total scores and WHO 5-item Well-Being Index (WHO5). Changes from baseline for primary efficacy end point were evaluated using adjusted mean difference with therapy, study and baseline value as a covariate at all timepoints.

**Results**: Analysis included 1873 patients (DVS, n= 956; placebo, n=917). Baseline characteristics were consistent across the 2 treatment arms, with 69% assigned into the ~~a~~nxious depressed group." Mean duration of the current depressive episode was 21.74 months (SD 44.086) and 35.3% <6 months. Mean baseline HAM-$D_{17}$ total score was 24.0; mean baseline HAM-$D_{17}$ A/S factor was 8.1. For most endpoints, DVS vs. placebo was highly statistically significant for LOCF. DVS improved HAM-$D_{17}$ total scores vs placebo (adjusted mean [95% CI] -1.72 [-2.35,-1.09]). MADRS total -2.35 (-3.24,-1.45); SDS total -1.78 (-2.47,-1.09); and WHO5 total: 1.10 (0.46,1.57), all $P$<0.001. There were significantly higher rates of response (47.0% vs 37.1%; $P$<0.001) and remission (25.2% vs 18.4%; $P$<0.001) on the HAM-$D_{17}$ with DVS; results were similar when baseline severity was defined by MADRS scores (response: 49.1% vs 37.1%; remission: 39.5% vs 30.5%; both $P$<0.001). DVS was associated with significantly better CGI-I and CGI-S scores compared with placebo (both $P$<0.001). Treatment emergent adverse events were reported by 78% and 69.5% of patients, and discontinuation due to any AEs was 3.6% and 3.1% (DVS vs placebo, respectively).

**Conclusions**: DVS 50 mg/d significantly improved depressive symptoms compared with placebo in a subpopulation of MDD patients with clinically relevant anxiety symptoms as defined by a HAM-$D_{17}$ A/S factor ≥7. Discontinuations due to AEs were similar for DVS and placebo.

**Learning Objectives:**

- To understand the efficacy and safety of desvenlafaxine (50 mg/d) when treating a subpopulation of patients with major depressive disorder and concurrent anxiety symptoms
- To understand the rates of remission and response in this subpopulation of patients when treated with desvenlafaxine (50 mg/d) compared with placebo

**Source Of Funding:** Research supported by Pfizer Inc.

**Literature References:**

- Thase ME, Kornstein SG, Germain JM, Jiang Q, Guico-Pabia C, Ninan PT. An integrated analysis of the efficacy of desvenlafaxine compared with placebo in patients with major depressive disorder. CNS Spectr 2009;14:144-154.
- Tourian KA, Jiang Q, Ninan PT. Analysis of the effect of desvenlafaxine on anxiety symptoms associated with major depressive disorder: pooled data from 9 short-term, double-blind, placebo-controlled trials. CNS Spectr 2010;15(3):187-193.

## ANALYSIS OF THE IMPACT OF FAMILY HISTORY SUBGROUPS ON DRUG PLACEBO SEPARATION AND PLACEBO RESPONSE ON TANDEM RATER AND COMPUTER OUTCOMES IN RCTS

Daniel DeBonis, BS[1], Jean Dries[1], Gary Sachs, MD[1,2]

[1]Bracket Global, Wayne, PA, [2]Massachusetts General Hospital, Boston, MA

**Introduction:** High placebo response is associated with clinical trial failure. Family history is considered a validator of psychiatric diagnosis, and is one factor to examine when researching placebo response in clinical trials.

**Methods:** We have examined patterns of placebo response in multiple depression (MDD and bipolar) studies to explore hypotheses regarding the failure of double-blind, RCT trials. Each trial also included tandem assessments of the primary outcome measure (MADRS or HAMD) administered by site-based raters (MADRSSBR or HAMDSBR) and independently assessed by computer (MADRSCOMP or HAMDCOMP) Placebo response was compared for subgroups reporting no reported family history of mood disorder (FHx(-)) and subjects reporting at least one first or secondary family member with a mood disorder (FHx(+)).

**Results:** In each trial, no significant differences were found between the placebo group and active treatment groups for both the rater and computer tandem assessments on any of the efficacy measures. Among FHx(-) subjects the Active vs placebo difference favored placebo in all 4 trials. This difference reached statistical significance based on MADRSCOMP or HAMDCOMP. but not MADRSSBR or HAMDSBR. in three of the four trials examined. Placebo response was numerically higher in the FHx(-) groups than in the FHx(+) groups across each study that was reviewed.

**Conclusion:** Our review of recent RCTs suggests high rates of placebo response in subjects reporting no family history of mood disorder may be a causal factor in failure of these efficacy studies. Further studies are needed to clarify which correlates of the FHx(-) subject status may be associated with high placebo response (e.g. diagnostic validity or enrollment rate).

**Learning Objectives:**

- Utility of family history as diagnostic validity
- Clinical trial methodologies

**Source Of Funding:** Bracket Global

**Literature References:**

- Nierenberg, A, et al. Family history of mood disorder and characteristics of major depressive disorder: A STAR D (sequenced treatment alternatives to relieve depression) study. Journal of Psychiatric Research Volume 41, Issues 3-4, April-June 2007, Pages 214-221.
- Feighner, J, et al. Diagnostic Criteria for Use in Psychiatric Research. Arch Gen Psychiatry. 1972 Jan;26(1):57-63.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## BIOMARKER HYPERMAPPING AS AN AID TO THE STRATIFICATION OF PATIENTS WITH DEPRESSION

John A. Bilello, BS, PhD, MS[1], Linda M. Thurmond, BS, PhD[1], Bo Pi, PhD[2]

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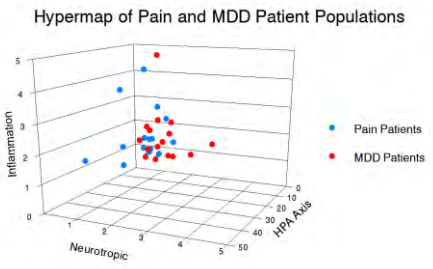
**Background:** The paradigm used for neuropsychiatric diagnosis and patient management is primarily based upon clinical interviews to stratify patients within adopted classifications. This paradigm has the caveat of not including information derived from biological or pathophysiological mechanisms. Our approach involves the construction of a multianalyte hypermap versus analyzing single markers either alone or in groups. Using clusters of biomarkers reflective of different physiologic parameters (e.g. HPA axis vs. metabolic vs. inflammatory markers), the patient's biomarker responses are mapped onto a multi-dimensional hyperspace.

**Methods:** Serum levels of 10 biomarkers (alpha-1 antitrypsin, Acylation Stimulating Protein, BDNF, Cortisol, EGF, Myeloperoxidase, Prolactin, Resistin, S100B and sTNFRII) were determined by immunoassay. Pathway specific coefficients previously generated from MDD patients were used to create the hyperspace vectors for subsets of MDD patients with comorbidities.

**Results:** We have used multiplex biomarker data from clinical samples to hyperspace map subjects with MDD and comorbidities including, diabetes, obesity, and chronic pain. In the experiment shown above, sera were evaluated from depressed patients with recurrent MDD with and without comorbid pain. Our results suggest, while populations are heterogeneous, that biomarker hypermapping can be useful in sub-classification of recurrent MDD and depressed pain patients. Several patients with chronic pain have patterns consistent with higher HPA axis activation.




**Conclusion:** Preliminary studies affirm the heterogeneity of depressed populations and suggested that biomarker hypermapping can aid in the sub-classification of patients. In addition to patient stratification, application of hypermapping could provide insights into the biomarker patterns associated with positive drug response or development of treatment resistance.

**Learning Objectives:**

- The paradigm used for neuropsychiatric diagnosis and patient management is primarily based upon clinical interviews to stratify patients within adopted classifications. We will provide data and insight into a new method to stratify and segregate populations of depressed subjects.
- Hypermaps further demonstrate that depressed populations are heterogeneous with regards to endophenotype.Use of biomarker pathway mapping can be useful in sub-classification of recurrent MDD and comorbidities including depressed pain patients.

**Source Of Funding:** Ridge Diagnostics Inc.

**Literature References:**

- Papakostas, G et al.Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a Pilot and Replication Study. Molecular Psychiatry , (13 December 2011) | doi:10.1038/mp.2011.166.
- Schmidt H, et al.Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology. 2011;36:2375-94.

## PREDICTORS OF RESPONSE & REMISSION WITH DESVENLAFAXINE 50 MG/D: A POOLED ANALYSIS OF RANDOMIZED, PLACEBO-CONTROLLED STUDIES IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Claudio N. Soares, MD, PhD[1], Rana S. Fayyad, PhD[2], Cedric O'Gorman, MD[2], Christine J. Guico-Pabia, MD[3]

[1]McMaster University & St. Joseph's Healthcare, Hamilton, Ontario, Canada, [2]Pfizer, Inc., New York, NY, [3]Pfizer, Inc., Collegeville, PA

**Background**: Early identification of likely responders to an antidepressant strategy may guide clinical treatment decisions, minimize the use of ineffective treatments and ultimately improve adherence and treatment outcomes for patients with major depressive disorder. In this study, data on age, gender, baseline depressive and functional measures, duration of current episode as well as improvements of depressive scores at earlier time points were examined to identify possible relevant predictors of treatment outcomes at 8 weeks among patients treated with desvenlafaxine (DVS) 50 mg/d or placebo.

**Methods**: Data were pooled from double-blind, fixed-dose studies in adult patients with a diagnosis of Major Depressive Disorder (MDD) based on DSM-IV or DSM-IV-TR. Patients were randomly assigned to DVS or placebo. Primary end point was change in HAM-D17 scores from baseline to week 8 (or last observation carried forward [LOCF]). A logistic regression model was used to examine the predictive value on response (defined as ≥50% improvement in HAM-D17 scores) or remission of depression (defined as an achievement of HAM-D17 scores ≤7) of the following variables: age, gender, baseline HAM-D17 total scores, baseline Sheehan Disability Scale total scores, duration of current episode and early HAM-D17 improvements (weeks 2, 3 and 4).

**Results**: DVS led to significant improvement of depression (HAM-D17 scores from baseline to study endpoint, response and remission) compared with placebo ($p<0.0001$), and was statistically significant for both the youngest (≤40 years of age) and the oldest (≥55 years of age) sub-groups. For the 41-54 years age group, DVS also produced significant improvement for both response and improvement in HAM-D17 scores, but not for remission. An equal or greater than 20% improvement on HAM-D17 scores at week 3 strongly predicted response (OR=9.37[7.23,12.15]) and remission (OR=14.7[9.39,23.01] of depression at week 8 (both $p<0.0001$). A positive predictive value (number of patients remitted at week 8 and with 20% improvement at week 3/those improved at week 3) indicated that 36% of patients that improved at week 3 also remitted at week 8. In addition, a negative predictive value (those who did not remit at week 8 nor improve at week 3/those who did not remit at week 3) showed that 96% of the patients who did not improve at week 3 also did not remit at week 8.

**Conclusions:** Clinical observations of patients' early response to the starting/recommended dose of DVS (50 mg/d), may have a clinical value in predicting further outcomes with this antidepressant agent and guide patient management.

**Learning Objectives:**

- To understand that identifying likely responders in patients with major depressive disorder treated with desvenlafaxine (50 mg/d) may guide clinical treatment decisions, and minimize the use of ineffective treatments
- To understand the positive and negative predictor values for remission and response in patients at week 3 and week 8 of treatment with desvenlafaxine (50 mg/d)

**Source Of Funding:** Research supported by Pfizer Inc.

**Literature References:**

- Szegedi A, Jansen WT, van Willigenburg APP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. J Clin Psychiatry 2009;70(3):344-353.
- Kuk AY, Li J, Rush AJ. Recursive subsetting to identify patients in the STAR*D: a method to enhance the accuracy of early prediction of treatment outcome and to inform personalized care. J Clin Psychiatry 2010;71(11):1502-1508.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## EARLY CLINICAL DEVELOPMENT OF THE OPIOID MODULATOR ALKS 5461 IN THE TREATMENT OF DEPRESSION AND ADDICTION

Elliot W. Ehrich, MD[1], Ryan Z. Turncliff, PhD[1], Edward M. Sellers, MD, PhD[2], Reese T. Jones, MD[3], Maurizio Fava, MD[4]

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The endogenous opioid system is thought to play a key role in the regulation of mood. Indeed, the "opium cure" was a pharmacologic mainstay of depression therapy prior to the advent of the tricyclic and monoamine oxidase inhibitor anti-depressants in the 1950's. The precise mechanism of endogenous opioids in mood regulation, however, is uncertain.

The contemporary use of opioids for depression is limited by abuse potential presumably a result of mu opioid agonism. ALKS 5461 consists of buprenorphine (BUP), a partial mu agonist, combined with ALKS 33, a counter-acting mu antagonist, co-formulated in a sublingual dosage form. The ALKS 33 component was designed to be minimally metabolized, highly potent, and sublingually bioavailable with the latter two properties being essential for sublingual co-formulation.

Initial clinical study of ALKS 33 included a remifentanyl challenge protocol in opioid-experienced volunteers. Oral 10 and 20 mg doses of ALKS 33 completely blocked mu agonist effects of serial pulses of remifentanyl as assessed by physiologic (pupilometry) and subjective VAS assessments (drug liking, high, etc.). Duration of blockade was >24 h following a single dose. Subsequently, a drug-drug interaction study was performed evaluating escalating doses of sublingual ALKS 33 co-administered with 8 mg BUP in a blinded fashion. In this study, 1 mg ALKS 33 caused a partial attenuation of mu effects whereas doses $\geq$4 mg yielded complete blockade.

A double-blind placebo controlled pilot study of once-daily sublingual ALKS 5461 was conducted in 32 patients with treatment resistant depression (TRD). Two dose ratios of BUP: ALKS 33 were evaluated: an 8:1 ratio (partial blockade of BUP mu agonist effects) and a 1:1 ratio (complete blockade). Efficacy was measured using the HAM-D-17 and the MADRS. Evidence of rapid efficacy was observed with both dose ratios at 7 days, with greatest efficacy at the 1:1 ratio, i.e. with complete mu blockade (p=0.032 and p=0.054; 1:1 ratio vs. placebo for HAM-D-17 and MADRS, respectively). ALKS 5461 was generally well tolerated. The most common AEs were dizziness, nausea, vomiting, and sedation, which occurred more frequently with the 8:1 ratio.

ALKS 5461 may represent a novel treatment for depression with a rapid onset. A larger phase II study is ongoing. Perturbation of the endogenous opioid system has also been linked to the development and propagation of addictive disorders. An ALKS 5461 – cocaine interaction study is ongoing.

**Acknowledgement**: Work funded in part by NIDA

**Learning Objectives:**

- Understand the therapeutic potential of combining counter-acting opioid receptor modulators for TRD and other disorders
- Understand the potential role of opioids in the regulation of mood

## LOWER CRONBACH'S ALPHA AT BASELINE THAN NEXT VISIT IN MDD STUDIES WITH AND WITHOUT SEPARATE INCLUSIONARY SCALES

Joan Busner, PhD[1], David G. Daniel, MD[2], Stuart A. Montgomery, MD[3], John J. Bartko, PhD[4]

[1]Penn State College of Medicine, and Bracket, Wayne, PA, [2]Bracket, Wayne, PA, [3]Imperial College of Medicine at St. Mary's Hospital in London, London W13 8WH, United Kingdom, [4]Biostatistical Consultant, Newville, PA

**Introduction:** Internal consistency of well-established efficacy scales such as the Montgomery Asberg Depression Rating Scale has been used as a proxy measure for raters' correct use of these measures. Improved internal efficacy scale consistency from baseline to endpoint has been demonstrated for MDD and schizophrenia when raters are monitored by various surveillance methodologies. Ratings inflation and poor ratings behavior at baseline (study entry) is a potential threat to study integrity and a putative contributor to poor signal detection in CNS trials. Separation of inclusionary scales from efficacy scales has been used as one strategy to preserve efficacy data from bias. To determine whether systematically poorer ratings behavior occurred at baseline than at subsequent visits on primary efficacy scale data (MADRS), we compared internal consistency of baseline and immediately following visit data (respective combined study visit Ns=1252 and 1144) from 2 large ongoing industry-sponsored MDD trials spanning 11 countries. In one study the MADRS value was inclusionary and in the other it was not.

**Method:** All available Baseline (N=1252) and Next Visit (N=1144) MADRS data from 2 ongoing MDD clinical trials were collected via eCRF and tested for internal consistency using Cronbach's alpha; across visit difference in internal consistency was compared. We examined the studies separately as a more stringent test and as a means of ascertaining whether the finding of one study would be replicated by the other.

**Results:** Study 1 (MADRS score not inclusionary): Baseline Cronbach's alpha was .59; next visit Cronbach's alpha was .82, $F(851,780) = 2.28$, $p < .0001$. Study 2 (MADRS score inclusionary): Baseline Cronbach's alpha was .38; next visit Cronbach's alpha was .65, $F(400,365) = 1.77$, $p < .001$.

**Discussion:** In two separate studies, ratings consistency of the primary efficacy measure at the baseline visit was significantly poorer than ratings consistency at the immediately subsequent visit. The finding occurred irrespective of whether the scale was or was not used as the baseline inclusion gatekeeper. As baseline efficacy scoring is a critical component of signal detection in CNS trials, detection of subpar baseline ratings practices, even when the measures have been divorced from inclusion values, demonstrates for the field the continued need for scoring scrutiny and intervention.

**Learning Objectives:**

- Recognize the role baseline internal scoring inconsistencies may play in MDD trial signal detection
- Become familiar with a method for detecting baseline internal scoring inconsistencies in blinded MDD trials

**Source Of Funding:** Bracket

**Literature References:**

- Khin NA; Chen Y; Yang Y; Yang P; Laughren TP: Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry 2011; 72(4):464–472.
- Busner J; McNamara C; Oakley M; Montgomery SA: Signal detection in adjunctive therapy trials for partially responsive major depressive disorder. Presentation at International Society for CNS Clinical Trials and Methodology (ISCTM), Baltimore, MD, 2010.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## LISDEXAMFETAMINE DIMESYLATE AUGMENTATION IN ESCITALOPRAM-TREATED ADULTS WITH MAJOR DEPRESSIVE DISORDER: ITEM ANALYSES OF DEPRESSIVE SYMPTOM SCALES

Robert Lasser, MD[1], Cynthia Richards, MD[1], Andrew J. Cutler, MD[2], Brooke Geibel[1], Ben Adeyi, MS[1], Brian Scheckner, PharmD[1], Angelo Sambunaris, MS[3], Ashwin A. Patkar, MD[4], Madhukar Trivedi, MD[5]

[1]Shire Development Inc., Wayne, PA, [2]Florida Clinical Research Center, LLC, Bradenton, FL, [3]Atlanta Institute of Medicine & Research, Atlanta, GA, [4]Duke University Medical Center, Durham, NC, [5]University of Texas Southwestern Medical School, Dallas, TX

**Purpose:** In a randomized, double-blind, placebo (PBO)-controlled trial, lisdexamfetamine dimesylate (LDX) augmentation of escitalopram monotherapy significantly reduced Montgomery-Asberg Depression Rating Scale (MADRS) total score versus PBO (least squares [LS] mean [90% CI] reduction from augmentation baseline to study endpoint in escitalopram nonremitters: -7.1 [-8.7, -5.6] vs -4.9 [-6.4, -3.3]; *P*=0.0902) at a prespecified alpha level of 0.10 in adults with major depressive disorder (MDD). We report post hoc MADRS and Hamilton Rating Scale for Depression-17 (HAM-D17) item analyses further assessing the effects of LDX.

**Methods:** Participants (18-55 y) with nonpsychotic MDD were included. After 8 weeks of open-label escitalopram, those with residual depressive symptoms (HAM-D17 score ≥4) were randomized to 6 weeks of LDX (20, 30, or 50 mg/d) or PBO augmentation. Descriptive data are presented in those defined as nonremitters (augmentation baseline MADRS total score >10) who took ≥1 randomized study drug dose and had ≥1 postrandomization MADRS assessment (LDX, n=65; PBO, n=64). Comparative statistical analyses were not performed as the study was not powered for these comparisons.

**Results:** The highest magnitude LS mean (90% CI) differences (LDX-PBO) for MADRS items were "inability to feel" (-0.7 [-1.0,-0.4]), "reported sadness"(-0.4 [-0.8, 0.0]), "lassitude" (-0.4 [-0.7, 0.0]), "concentration difficulties" (-0.4 [-0.7, 0.0]), and "apparent sadness" (-0.3 [-0.6, 0.0]). For the HAM-D17, "work and interests"(-0.5 [-0.7, -0.3]) and "suicidal impulses" (-0.1 [-0.1, 0.0]) met this criterion.

**Conclusions:** These results identify items that may be improved by LDX. Further research is needed to identify responsive symptom domains.

**Learning Objectives:**

- Understand the rationale for psychostimulant augmentation therapy in MDD
- Describe the effectiveness of lisdexamfetamine augmentation therapy in adults with MDD

**Source Of Funding:** Shire Development Inc.

**Literature References:**

- Trivedi M et al. Efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with major depressive disorder treated with an antidepressant. Poster presented at: American Psychiatric Association 164th Annual Meeting. May 14-18, 2011; Honolulu, HI.
- Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382-389.

## EFFECTS OF THE D-AMPHETAMINE PRODRUG, LISDEXAMFETAMINE DIMESYLATE, AND ANTIDEPRESSANT MEDICATIONS ON THE PORSOLT BEHAVIORAL DESPAIR TEST IN MICE

Jann Nielsen, PhD[1], Vincent Castagné, PhD[2], David Hackett, MS[3], Peter Hutson, PhD[1]

[1]Shire Pharmaceuticals, Wayne, PA, [2]Porsolt, Le Genest-Saint Isle, Boulogne-Billancourt, France, [3]Shire Development Inc Ltd, Chineham, Basingstoke, United Kingdom

**Objectives:** To examine the effects of lisdexamfetamine dimesylate (LDX) and clinically effective antidepressants in the Porsolt Behavioral Despair Test.

**Methods:** Using the Porsolt Behavioral Despair Test in mice, duration of immobility over the final 4 min of a 6-min forced swim was measured. NMRI mice (10/group) were orally dosed 60-90 min prior to testing with LDX (1-32mg/kg); selective serotonin reuptake inhibitors (SSRIs), escitalopram (2-32mg/kg), sertraline (4-64mg/kg), or fluoxetine (20-80mg/kg); serotonin-norepinephrine reuptake inhibitors (SNRIs), venlafaxine (8-64mg/kg) or duloxetine (8-64mg/kg); an atypical antidepressant, bupropion (5-40mg/kg); the tricyclic antidepressant as reference substance, imipramine (128mg/kg); or vehicle. Outcomes are reported as percent difference in duration of immobility for optimal doses vs vehicle.

**Results:** Compared with vehicle, LDX produced significant (P<.05) decreases in immobility at doses of 16 and 32mg/kg of 23%-51%. Likewise, maximally effective doses of escitalopram (32mg/kg), fluoxetine (80mg/kg), and sertraline (32mg/kg) produced decreases of 64%, 27%, and 31%, respectively. Venlafaxine (16mg/kg) and duloxetine (64mg/kg) produced decreases of 50% and 38%, respectively. Bupropion (40mg/kg) produced a decrease of 33%. Imipramine (128mg/kg) produced decreases of 48%-74%.

**Conclusion:** LDX demonstrated antidepressant activity in a preclinical animal model. The magnitude of LDX effects was consistent with those seen with SSRIs, SNRIs, and atypical antidepressants.

**Learning Objectives:**

- Describe the effects of lisdexamfetamine dimesylate (LDX) on immobility in the Porsolt Behavioral Despair Test, an important animal screening test for antidepressant medications
- Assess the effects of LDX in relation to several clinically effective antidepressant medications of various classes

**Source Of Funding:** Research was funded by the sponsor, Shire Development Inc.

**Literature References:**

- Porsolt RD, Bertin A, Jalfre M: Behavioral despair in mice: a primary screening test for antidepressants. Archives Internationales de Pharmacodynamie et de Thérapie 1977;229:327-336.
- Vaugeois J M, Pouhé D, Zuccaro F, Costentin J. Indirect dopamine agonists effects on despair test: dissociation from hyperactivity. Pharmacol Biochem Behav 1996;54:235-239.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## AUGMENTATION WITH THE D-AMPHETAMINE PRODRUG, LISDEXAMFETAMINE DIMESYLATE, OF ANTIDEPRESSANT MEDICATIONS: EFFECT ON THE PORSOLT BEHAVIORAL DESPAIR TEST IN MICE

David Hackett, MS[1], Vincent Castagné, PhD[2], Peter Hutson, PhD[3]

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**Objectives:** To examine augmentation of clinically effective antidepressants with lisdexamfetamine dimesylate (LDX) in the Porsolt Behavioral Despair Test.

**Methods:** Duration of immobility over 4 min of a forced swim was measured. NMRI mice (10/group) were orally dosed 60-90 min before testing with LDX (<=32mg/kg) plus a selective serotonin reuptake inhibitor (SSRI): escitalopram (<=8mg/kg), sertraline (<=32mg/kg), or fluoxetine (<=80mg/kg); a serotonin-norepinephrine reuptake inhibitor: venlafaxine (<=8mg/kg) or duloxetine (<=16mg/kg); or an atypical antidepressant, bupropion (40mg/kg). For augmentation studies, doses were selected as those minimally effective or subeffective when given alone. Outcomes are reported as percent decrease in duration of immobility for highest doses of LDX plus antidepressant vs vehicle, LDX alone, and antidepressant alone. Augmentation was defined as a significant difference (P<.05) between the same dose of antidepressant alone and in conjunction with LDX in the same study.

**Results:** LDX was observed to augment the effect of escitalopram, sertraline, venlafaxine, and bupropion but not fluoxetine or duloxetine.
Conclusion: Although comprehensively validated for single-drug assays, this preclinical model has been less extensively evaluated for sensitivity in augmentation studies. Nonetheless, these data suggest the potential for efficacy of LDX augmentation of antidepressant treatment, a finding supported by recent clinical trials in adults with major depressive disorder.

**Learning Objectives:**

- Describe effects of antidepressant augmentation with lisdexamfetamine dimesylate (LDX) on immobility in the Porsolt Behavioral Despair Test
- Assess effects of augmentation with LDX in relation to various anti-depressant classes

**Source Of Funding:** Research was funded by the sponsor, Shire Development Inc.

**Literature References:**

- Porsolt RD, Bertin A, Jalfre M: Behavioral despair in mice: a primary screening test for antidepressants. Archives Internationales de Pharmacodynamie et de Therapie 1977; 229:327-336.
- Trivedi MH, Cutler A, Richards C, et al: Efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with major depressive disorder treated with an antidepressant. Poster presented at: American Psychiatric Association's 164th Annual Meeting; May 14-18, 2011; Honolulu, HI.

## EFFICACY OF RIGHT UNILATERAL ULTRABRIEF PULSE ELECTROCONVULSIVE THERAPY (ECT): DATA FROM PHASE 1 OF THE PRIDE STUDY

Charles H. Kellner, MD[1], Mustafa M. Husain, MD[2], Rebecca G. Knapp, PhD[3], W. Vaughn McCall, MD, MS[4], Georgios Petrides, MD[5], Shirlene M. Sampson, MD, MS[6], Robert C. Young, MD[7], Robert M. Greenberg, MD[8], Shawn M. McClintock, PhD, MS[2], Martina Mueller, PhD[3], Kristen G. Tobias, BS[1], Richard D. Weiner, MD, PhD[9], Mimi C. Briggs[1], Rosa M. Pasculli[1], Sarah H. Lisanby, MD[9]

[1]Mount Sinai School of Medicine, New York, NY, [2]UT Southwestern Medical Center, Dallas, TX, [3]Medical University of South Carolina, Charleston, SC, [4]Wake Forest University School of Medicine, Winston-Salem, NC, [5]The Zucker Hillside Hospital, Northshore-LIJ Health System, New York, NY, [6]Mayo Clinic, Rochester, MN, [7]Weill Cornell Medical College, White Plains, NY, [8]Lutheran Medical Center, Brooklyn, NY, [9]Duke University School of Medicine, Durham, NC

Among the refinements to electroconvulsive therapy (ECT) technique are right unilateral electrode placement (RUL) and ultrabrief pulse (UBP) stimuli. Both of these refinements are intended to reduce the cognitive effects of ECT; however, there are insufficient published data to confirm that, when used together, they adequately preserve antidepressant efficacy in the elderly population.

Prolonging Remission in Depressed Elderly (PRIDE) is an ongoing clinical trial in which unipolar depressed patients, 60 years old and older, are given an acute course of RUL UBP ECT augmented with venlafaxine (Phase I). Remitters are then randomized to one of two active continuation treatment groups for six months: 1) venlafaxine plus lithium or 2) venlafaxine plus lithium plus a flexible schedule of additional continuation ECT (Phase II). Depression severity is assessed by the Hamilton Rating Scale for Depression, 24-item ($HRSD_{24}$). Neurocognitive functioning is assessed at baseline and throughout the study by a comprehensive assessment battery. We present antidepressant efficacy data on 97 patients entered into PRIDE during the period February 2010 through December 1, 2011; three of these subjects were still active as of December 1, 2011 and were not considered in outcome assessments.

Approximately 62% of patients remitted ($HRSD_{24} \leq 10$ on two consecutive measurements), 7.5% were non-remitters (failed to reach remission criteria after ≥12 ECT), and 30% were dropouts (did not meet remission criteria and received <12 ECT).

The mean baseline $HRSD_{24}$ score was 31.0 (sd 7.7). The final $HRSD_{24}$ was 11.1 (sd 8.9), with a highly statistically significant reduction in $HRSD_{24}$ score from baseline (95% CI: 16.6 to 21.6, n=94) [p<0.0001, paired t-test]. Among remitters only (n=58), the final $HRSD_{24}$ was 6.3 (sd 2.4), as compared to 18.9 (sd 4.1) among nonremitters (n=7) and 22.0 (sd 8.4) among dropouts (n=28). The mean number of ECT was 7.4 (sd 2.9) among remitters, 12.2 (sd 3.0) among nonremitters, and 6.2 (sd 3.0) among dropouts.

These data add to the growing body of literature demonstrating satisfactory antidepressant efficacy of RUL UBP ECT, including in the geriatric population. Subsequent data from Phase I of the PRIDE study will also inform the field regarding the cognitive effect profile of RUL UBP ECT in depressed geriatric patients.

**Learning Objectives:**

- To understand that modern ECT technique continues to be refined, with choices available for electrode placement and stimulus parameters.
- To understand that emerging data suggest satisfactory efficacy of right unilateral ultrabrief pulse ECT in elderly patients.

**Source Of Funding:** NIMH 5U01 MH055495

**Literature References:**

- Kellner CH, et al. Bifrontal, bitemporal, and right unilateral electrode placement in ECT: randomised trial. Br J Psychiatry 2010;196: 226-34.
- Lisanby SH. Electroconvulsive therapy for depression. N Engl J Med 2007;357: 1939-45.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## ITEM ANALYSES OF LISDEXAMFETAMINE DIMESYLATE AUGMENTATION EFFECTS ON DEPRESSIVE SYMPTOMS IN ADULTS WITH MAJOR DEPRESSIVE DISORDER

Manisha Madhoo, MD[1], Richard S.E. Keefe, PhD[2], Robert M. Roth, PhD[3], Angelo Sambunaris, MD[4], James Wu, PhD[1], Madhukar Trivedi, MD[5], Colleen S. Anderson, Other[1], Robert Lasser, MD[1]

[1]Shire Development Inc., Wayne, PA, [2]Duke University Medical Center, Durham, NC, [3]Dartmouth Medical School, Lebanon, NH, [4]Atlanta Institute of Medicine & Research, Atlanta, GA, [5]University of Texas Southwestern Medical School, Dallas, TX

**Purpose:** Lisdexamfetamine dimesylate (LDX) augmentation of selective serotonin reuptake inhibitor (SSRI) monotherapy significantly improved executive function on the Behavior Rating Inventory of Executive Function-Adult Version self-report (BRIEF-A; primary endpoint) and depressive symptoms on the Montgomery-Asberg Depression Rating Scale (MADRS; secondary endpoint) versus placebo (PBO) in adults with major depressive disorder in partial or full remission. We present post hoc MADRS item analyses to further examine LDX effects.

**Methods:** Adults (18-55 y) with MADRS total scores ≤18 and BRIEF-A Global Executive Composite T-scores ≥60 on ≥8 weeks of SSRI monotherapy were eligible for this study. After 2 weeks of screening, participants were randomized to 9 weeks of double-blind LDX (wk 1: 20 mg/d; wks 2-6: titrate to optimal dose in 10-mg weekly increments [maximum, 70 mg/d]; wks 7-9: maintain optimized dose) or PBO augmentation, followed by 2 weeks of single-blind placebo. Descriptive data are presented for randomized participants who took ≥1 study drug dose and had ≥1 postbaseline BRIEF-A assessment (PBO, 72; LDX, 71); the study was not powered for statistical assessment of these item analyses.

**Results:** Mean±SD MADRS total scores were reduced at study endpoint (PBO, -2.9±5.44; LDX,-5.1±5.94); the least squares (LS) mean (95% CI) treatment difference favored LDX (-1.9 [-3.7, 0.0]; *P*=0.0465). The highest magnitude LS mean (95% CI) differences (LDX-PBO) were concentration difficulties (-1.0 [-1.5, -0.5]), lassitude (-0.6 [-1.1, -0.2]), pessimistic thoughts (-0.3 [-0.6, 0.0]), and reduced appetite (0.3 [0.0, 0.6]); item changes based on baseline MADRS total score (<10 or ≥10) showed similar trends.

**Conclusion:** The results identify specific items improved by LDX, providing direction for future research.

**Learning Objectives:**
- Understand the rationale for psychostimulant augmentation in MDD
- Describe the effects of lisdexamfetamine augmentation in MDD

**Source Of Funding:** Shire Development, Inc.

**Literature References:**

- Trivedi M et al. Efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with major depressive disorder treated with an antidepressant. Presented at: American Psychiatric Association 164th Annual Meeting. May 14-18, 2011; Honolulu, HI.
- Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382-389.


## A NOVEL V1A RECEPTOR ANTAGONIST AND POTENTIAL ANTIDEPRESSANT, SRX246, BLOCKS VASOPRESSIN MEDIATED EFFECTS ON STRESS & FEAR: AN FMRI STUDY

Neal G. Simon, PhD[1,2], Royce Lee, MD[3], Michael J. Brownstein, MD, PhD[1], Emil Coccaro, MD[3]

[1]Azevan Pharmaceuticals, Inc, Bethlehem, PA, [2]Lehigh University, Bethlehem, PA, [3]University of Chicago, Chicago, IL

**Background:** SRX246 is a novel vasopressin 1a receptor antagonist that is efficacious in animal models of depression and other stress-related disorders. The drug has completed Phase I Single Ascending Dose (SAD) and 14-day Multiple Ascending Dose (MAD) Clinical Trials with excellent safety, tolerability, and pharmacokinetics.

**Purpose:** Use fMRI to determine if orally administered SRX246 can block the effects of intranasally administered vasopressin (AVP) on the brain response to threatening emotional stimuli in healthy volunteers. Previous studies have shown effects of AVP signaling on the amygdala and other brain structures involved in the neural processing of social and emotional cues, including the temporoparietal junction, subgenual cingulate, and connected structures. Reactivity to stimuli such as emotional faces in these brain regions has been linked to major depressive disorder

**Method:** All study procedures were approved by the Institutional Review Board of The University of Chicago. The subjects (n=29 males aged 18-55) provided informed consent and met the inclusion criteria. A baseline fMRI scan was acquired before randomization to oral SRX246 (120mg PO BID; n=15) or placebo (n=14) for 5-10 days, after which subjects returned for a second scanning session. At Session 2, subjects within the SRX246 and placebo groups were randomized again to either intranasal vasopressin (Pitressin 40 IU) or placebo. The implicit processing of emotional facial expressions (Ekman faces; Angry, Neutral, Happy) was tested while fMRI data were acquired.

**Results:** SRX246 treatment (120 mg PO BID) significantly blunted the increased BOLD signal seen in response to angry faces following intranasal vasopressin in the right temporoparietal cortex, specifically Brodmann Area 39. SRX246 treatment also significantly blunted the BOLD signal to angry faces in the medial prefrontal cortex, including the anterior cingulate cortex, in comparison to placebo treatment.

**Conclusion:** These findings demonstrate that amplification of circuit function by vasopressin during task performance is blunted by SRX246, showing that the drug enters brain and acts on vasopressin receptors. SRX246 blunted effects of intranasal vasopressin on BOLD signal change in response to angry faces in the amygdala, temporoparietal cortex, and anterior cingulate. These data provide proof-of-mechanism for SRX246 and also indicate potential novel actions the compound on regional brain reactivity to social and emotional stimuli highly relevant to major depressive disorder.

**Financial Support:** NIH Award MH-063663 and Azevan Pharmaceuticals, Inc.

**Learning Objectives:**
- Enhance knowledge of vasopressin receptor antagonist effects in the brain
- Understand a novel approach to studying now vasopressin modulates neural responses to emotional stimuli
- Assess the potential utility of a novel antidepressant using fMRI

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## FUNCTIONAL CONNECTIVITY OF THE DEFAULT MODE NETWORK IN PERSON WITH DYSTHYMIC DISORDER: A RESTING STATE FMRI STUDY

Jonathan Posner, MD, Bradley Peterson, MD, Inbal Gat, BS, Anna Mechling, BS, David Hellerstein, MD

Columbia University, New York, NY

**Objective:** We aimed to investigate the pathophysiology of dysthymic disorder (DD) by examining the architecture of the brain's default mode network (DMN) in a population of medication-free adults with DD. The DMN is a collection of brain regions that reliably deactivate during goal-directed behaviors (1). Neural activity in one brain region within the DMN strongly correlates over time with activity in other brain regions within the DMN. Because prior studies describe atypical connectivity within the DMN in adults with MDD (2), we aimed to determine whether this anomaly generalizes to dysthymia or whether it is specific to MDD.

**Methods:** We used resting-state functional MRI to assess the functional connectivity of the DMN in adults with DD (N=41) and in healthy control participants (N=25). Two 5-minute resting-state scans were obtained for each subject. We used standard image preprocessing methods, employing SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) with the conn_toolbox (http://www.nitrc.org/projects/conn) for functional connectivity analysis.

**Results:** We found that functional connections within the brain's DMN were greater in persons with DD compared with controls. We confirmed this finding using a social network analysis that calculated the density of connections within the DMN. Exploratory analyses revealed the connection strength between the posterior cingulate cortex, a central node in the DMN, and the amygdala was a strong predictor of HAM-D scores (left amygdala; r=0.65; p<0.001; right amygdala; r=0.58; p<0.001).

**Conclusions:** The findings in DD are consistent with those found in patients with MDD and suggest that increased connectivity within the DMN may be important in the pathophysiology of both acute and chronic manifestations of depressive illness. Moreover, that increased connectivity between the DMN and the amygdala strongly predicts depressive symptoms suggests a potentially important target for novel therapeutics.

**Learning Objectives:**

- The audience was gain familiarity with resting state functional connectivity MRI analysis and the brain's default mode network
- The audience will learn about anomalies in the brain's default mode network in individuals with dysthymic disorder

**Source Of Funding:** Eli Lilly Corporation; NIMH Grant K23-MH091249 (JP)

**Literature References:**

- Raichle M, et al. A default mode of brain function: a brief history of an evolving idea. NeuroImage. 2007;37(4):1083-90.
- Sheline YI, et al. The default mode network and self-referential processes in depression. Proceedings of the National Academy of Sciences. 2009;106(6):1942.

## SEXUAL SATISFACTION IN MAJOR DEPRESSIVE DISORDER BEFORE AND AFTER TREATMENT WITH SSRI IN THE STAR*D STUDY

Waguih William IsHak, MD, Scott Christensen, BS

Cedars-Sinai Medical Center and UCLA, Los Angeles, CA

**Background:** Major Depressive Disorder (MDD) is a highly prevalent psychiatric illness that significantly affects mood, sexual satisfaction, and quality of life (QOL). The first line treatment for MDD is Selective Serotonin Reuptake Inhibitors (SSRIs). SSRIs have been associated with sexual dysfunction, which often compromises patient medication compliance and QOL. We examined the impact of MDD and SSRI treatment for MDD on sexual satisfaction and QOL in efforts to help physicians better address SSRI associated sexual side-effects.

**Methods:** We analyzed baseline and post-treatment data for 2,324 patients with MDD that completed treatment with citalopram, an SSRI, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. We focused on three outcome measures: severity of depression, QOL, and sexual satisfaction as measured by the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and Q-LES-Q item#9, respectively.

**Results:** Impairment in sexual satisfaction (ISS) was reported in 63.8% of patients before and 46.8% after treatment (p<0.0001). Less severely depressed patients experienced less ISS before and after treatment. Males who did not achieve remission from MDD with citalopram had an ISS prevalence of 62.1% as compared to 20.5% (P< 0.0001) in males that achieved remission. Similarly, the prevalence of ISS was 60.7% in females that did not achieve remission compared to 21.9% (P< 0.0001) of females that achieved remission. Regression models showed that depressive symptom severity predicted ISS (p<0.0001), and that the latter predicted impairment in QOL (p<0.0001).

**Conclusions:** Citalopram treatment significantly improved sexual satisfaction and QOL, especially in patients who achieved remission. These results highlight the need for physicians to be cognizant of patient sexual satisfaction and to treat MDD rigorously until remission.

**Learning Objectives:**

- Learn the difference between the Sexual Satisfaction and Sexual Dysfunction
- Understand the concept of Sexual Satisfaction and how to measure it
- Acquire knowledge about how to improve Sexual Satisfaction in treatment of Major Depression
- Appreciate the importance of treating depression to remission and impact on sexual satisfaction and QOL

**Source Of Funding:** Original Study: NIMH Contract # N01MH90003 to the University of Texas Southwestern Medical Center. Current analysis: none.

**Literature References:**

- Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G. STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials. 2004;25:119-42.
- IsHak WW, Greenberg JM, Balayan K, Kapitanski N, Jeffrey J, Fathy H, Fakhry H, Rapaport MH. Quality of life: the ultimate outcome measure of interventions in major depressive disorder. Harv Rev Psychiatry. 2011 Sep-Oct;19(5):229-39.
- Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. J Clin Psychiatry. 2006;67(6): 33–7.
- Daly EJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Gaynes BN, Warden D, Morris DW, Luther JF, Farabaugh A, cook I, Rush AJ. Health-related quality of life in depression: a STAR*D report. Ann Clin Psychiatry. 2010;22(1):43-55.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## SYMPTOMATIC AND COGNITIVE RESPONSE TO TREATMENT IN DEPRESSION

Paul Maruff, PhD[1], Peter Snyder, PhD[2], Robert Pietrzak, PhD[3]

[1]University of Melbourne, Melbourne, Australia, [2]Lifespan Affiliated Hospitals, Providence, RI, [3]Yale University, New Haven, CT

**Background:** Clinical trials of treatments for major depression usually rely on clinician or patient ratings of symptoms but there is growing interest in the potential for cognitive measures to become objective measures of treatment response.

**Aim:** To investigate whether neuropsychological changes could be useful early indicators of treatment response and/or overall indicators of treatment response in major depression.

**Method:** Fifty recently admitted in patients with depression (mean age = 38.2 SD = 5.4, 32% female, mean Montgomery-Asberg Depression Rating Scale (MADRS) score = 37.2; SD=7.6, 18% not currently taking antidepressant medication) and 50 matched healthy controls completed a CogState computerized test battery which included measures of attention and processing speed, verbal memory visual memory and executive function at admission and then 3 and 6 weeks after admission. The MADRS was used to rate the severity of depressive symptoms at each assessment.

**Results:** Statistically significant impairment of a moderate magnitude was evident at baseline in depressed patients compared with healthy controls on all cognitive measures with the largest impairments present in processing speed, verbal memory, visual memory and executive function. Treatment response was defined as a 50% or greater reduction on the MADRS from baseline to the 6 week assessment. No improvement in cognitive function was evident at the 3 week assessment in responders. After six weeks of treatment, performance on the measures of verbal memory and psychomotor function improved in responders. Impairments in executive function and visual memory remained in responders.

**Conclusion:** Despite significant impairment in neuropsychological functioning in this these individuals with depression, the findings suggest that specific aspects of cognitive function such as processing speed and verbal memory are related to treatment response.

**Learning Objectives:**

- To understand relationship between depressive symptoms and cognitive function
- Appreciate which aspects of cognitive function improve with follwing treatment with antidepressants

**Source Of Funding:** None

**Literature References:**

- Douglas KM, Neuropsychological changes and treatment response in severe depression. Br J Psychiatry. 2011 Feb;198(2):115-22.
- Pietrzak RH, A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. J Clin Exp Neuropsychol. 2009, 7:848-59.

## VASOPRESSINERGIC MODULATION OF EMOTION: A PILOT FMRI STUDY

Royce J. Lee, MD[1], Emil F. Coccaro, MD[1], Shi Fang Lu, PhD[2,3], Christophe Guillon, PhD[2,3], Karine Fabio, PhD[2,3], Brownstein Michael, MD[3], Neal Simon, MD[2,3]

[1]The University of Chicago, Chicago, IL, [2]Lehigh University, Bethlehem, PA, [3]Azevan, Bethlehem, PA

**Background:** Although modulation of neural activity by central V1a and V1b receptors is the presumed mechanism by which centrally released vasopressin may alter behavior (1), to date this has been difficult to study in humans. Previous work has indicated that limbic, frontal, and parietal brain function may be modulated by intranasally administered vasopressin (2). It was hypothesized that a novel orally administered vasopressin V1a receptor antagonist (SRX246) would modulate neural activity during viewing of angry faces as measured by fMRI Blood Oxygen Level Dependent (BOLD) signal in opposition to exogenous vasopressin administered intranasally.

**Methods:** 29 healthy, medication free male adults were randomized in double-blind fashion to 5-10 days of SRX251 (120mg BID) or placebo. fMRI BOLD response to angry faces versus control (fixation point and happy faces) was measured at baseline and after 5 - 10 days of oral drug, 45 minutes after randomized, double-blind intranasal administration of 40 IU vasopressin or placebo.

**Results:** Voxelwise whole brain analysis revealed that SRX246 was associated with decreased BOLD signal intensity to angry faces in left and right temporoparietal junction (BA39), anterior cingulate, and dorsal cingulate ($p < .005$). ANCOVA of extracted signal intensity in anatomical ROIs of left temporoparietal junction (BA39), anterior cingulate, and dorsal cingulate , covarying for baseline signal intensity, confirmed significant associations of SRX246 with decreased BOLD response in these regions to angry faces. The effects of SRX246 did not appear to overlap with regional effects of intranasal vasopressin.

**Conclusion:** Preliminary evidence was found for an effect of a novel vasopressin V1a antagonist on brain response to angry faces. Further work is needed to confirm the regional specificity of these effects and extend them to groups that have abnormal brain response to socially agonistic stimuli.

**Learning Objectives:**

- Understand a novel approach to studying vasopressinergic modulation of human brain response to social cues.
- Become familiar with new knowledge regarding human central vasopressin function.

**Source Of Funding:** Azevan Pharmaceuticals

**Literature References:**

- Ferris C; Imaging the neural circuitry and chemical control of aggressive motivation. BMC Neuroscience 2008; 9; 111.
- Zink C, et al. Vasopressin modulates social recognition-related activity in the left temporoparietal junction in humans.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## CLINICAL DEVELOPMENT OF THE NOREPINEPHRINE REUPTAKE INHIBITOR EDIVOXETINE (LY2216684 HCL) FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: USE OF PHARMACOKINETICS, PHARMACODYNAMICS AND BIOMARKERS

William Kielbasa, PhD[1], Tonya Quinlan, BS[1], Debra Luffer-Atlas, PhD[1], Malcolm I. Mitchell[2], Eshetu Wondmagegnehu, PhD[1], Michael A. Turik, MD[1], Mary Anne Dellva, MS[1], Sanjay Dube, MD[1], Celine Goldberger, MD[1]

[1]Eli Lilly and Company, Indianapolis, IN, [2]Lilly Research Centre, Surrey, United Kingdom

Current treatment recommendations for major depressive disorder (MDD) focus on selective serotonin reuptake inhibitors (SSRIs) as a first-line treatment. While SSRIs have demonstrated efficacy, response to treatment is varied with approximately only one-third of patients meeting criteria for remission. Symptoms of depression may also involve dysregulation of noradrenergic neurotransmission. Edivoxetine (2-Morpholinemethanol, α-[(5-fluoro-2-meth-oxyphenyl) methyl]-α-(tetrahydro-2H-pyran-4-yl)-, hydrochloride, (αR, 2S) is a potent inhibitor of the norepinephrine transporter. Phase 1 studies were conducted to characterize edivoxetine pharmacokinetics (PK) and pharm-acodynamics (PD). In a PK drug interaction study in healthy adults, paroxetine mildly increased the exposure of edivoxetine, presumably due to chemical inhibition of the cytochrome P450 (CYP) 2D6 enzyme, suggesting that CYP2D6 is partly involved in the metabolism of edivoxetine. However, edivoxetine appears to depend less on the CYP2D6 enzyme for metabolism than atomoxetine and is likely to have less exposure variability in patients with diverse CYP2D6 polymorphism. Peripheral (plasma) and central (cerebrospinal fluid, CSF) NET inhibition using 3,4-dihydroxyphenylglycol (DHPG) as a biomarker of pharmacologic activity was evaluated to inform edivoxetine dose selection for efficacy trials. In healthy adults, edivoxetine decreased plasma and CSF DHPG concentrations suggestive of NET inhibition. Based on PK/PD modeling and simulation, a nonlinear dose – effect relationship for plasma and CSF DHPG was revealed; however, higher edivoxetine doses led to a greater reduction from baseline of CSF DHPG ($I_{MAX, CSF}$ = 75%) compared to plasma DHPG ($I_{MAX, PLASMA}$ = 35%). The dissimilar effects on peripheral and central DHPG suggest that CSF DHPG might be a more sensitive and representative biomarker for central target engagement than plasma DHPG. The PK/PD model provided insights about edivoxetine pharmacology and may serve as a relevant predictor of an effective dose. A dose range of 6 – 18 mg investigated the efficacy of edivoxetine in MDD as monotherapy and adjunctive treatment to a SSRI. In both studies, edivoxetine was generally well-tolerated and demonstrated the potential to be an effective drug to treat MDD.

**Learning Objectives:**

- To present how PK was used to inform clinical development of edivoxetine.
- To present how PD was used to inform clinical development of edivoxetine.
- To present how biomarkers were used to inform clinical development of edivoxetine.

## A POOLED ANALYSIS OF VILAZODONE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: EFFICACY ACROSS SYMPTOMS

Arif Khan, MD[1], Wenjie Song, PhD[2], John Edwards, MD[2], Adam Ruth, PhD[3]

[1]Duke University School of Medicine / Northwest Clinical Research Center, Bellevue, WA, [2]Forest Research Institute, Jersey City, NJ, [3]Prescott Medical Communications Group, Chicago, IL

**Objective:** Vilazodone, a serotonin reuptake inhibitor and 5-$HT_{1A}$ receptor partial agonist, is approved by the US Food and Drug Administration for the treatment of MDD in adults. Efficacy and safety were established in two 8-week, double-blind, randomized, placebo-controlled pivotal trials (RCT-1: NCT00285376; RCT-2: NCT00683592).

**Methods:** Data from RCT-1 and -2 were pooled to analyze the effects of vilazodone versus placebo. Patients 18-70 years of age with DSM-IV-TR–defined MDD and a minimum score ≥22 on the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) participated. Study design was similar in both trials (a 1-week screening period followed by 8-week double-blind treatment). Patients randomized to vilazodone were titrated to a target dose of 40 mg, taken once daily (QD) with food, over a 2-week period (10 mg QD for 7 days, 20 mg QD for the next 7 days, and 40 mg QD thereafter). The primary efficacy parameter (change from baseline to Week 8 in Montgomery-Asberg Depression Rating Scale [MADRS] total score) was analyzed using an analysis of covariance (ANCOVA) model based on the intent-to-treat (ITT) population and the last observation carried forward (LOCF) approach. Secondary efficacy endpoints included $HAMD_{17}$, Clinical Global Impressions-Improvement (CGI-I) and -Severity (CGI-S), Hamilton Anxiety Rating Scale (HAMA), response (MADRS ≥50% improvement from baseline; $HAMD_{17}$ ≥50% improvement from baseline; CGI-I score ≤2) and remission (MADRS ≤10). Change from baseline on MADRS single items and remission MADRS ≤12 were also evaluated.

**Results:** The ITT population comprised 432 vilazodone- and 431 placebo-treated patients. Vilazodone significantly improved MADRS scores relative to placebo; the least squares mean difference (LSMD [95% CI]) was -2.79 (-4.14, -1.44) (*P*<.0001). Significant improvement on all secondary measures in favor of vilazodone was also seen (*P*<.01). Response for vilazodone vs placebo based on MADRS and $HAMD_{17}$ ≥50% improvement was 42% vs 29% (*P*=.0002) and 44% vs 33% (*P*=.0007), respectively; CGI-I response was 49% vs 35% (*P*<.0001). Remission for vilazodone vs placebo using MADRS ≤10 and ≤12 criteria was 29% vs 20% (*P*=.0041) and 35% vs 22% (*P*<.0001), respectively. Significant improvement in favor of vilazodone versus placebo was seen on change from baseline in every MADRS single item (LSMD): apparent sadness, -0.24; reported sadness, -0.29; inner tension, -0.31; reduced sleep, -0.30; reduced appetite, -0.20; concentration difficulties, -0.24; lassitude, -0.27; inability to feel, -0.25; pessimistic thoughts, -0.35; suicidal thoughts, -0.29 (*P*<.01 for all).

**Conclusion:** Pooled data from 2 pivotal trials demonstrated significantly higher rates of response and remission for vilazodone treatment relative to placebo. Vilazodone was significantly superior to placebo on all depression rating scales tested and showed efficacy on all MADRS single items.

**Learning Objectives:**

- At the conclusion of this session, participants should be able to evaluate the efficacy of vilazodone across the symptom domains of MDD.
- At the conclusion of this session, participants should be able to evaluate symptom improvement relative to several clinically relevant thresholds.

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

**Literature References:**

- Khan A: 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: 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.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## CYTOCHROME P-450 2D6 POOR VERSUS EXTENSIVE PHENOTYPES: COMPARING CLINICAL CHARACTERISTICS ON AN INPATIENT PSYCHIATRY MOOD DISORDERS UNIT

Simon Kung, MD, Maria I. Lapid, MD, Emily K. Johnson, Michael N. Govrik, Manuel E. Fuentes Salgado, MD

Mayo Clinic, Rochester, MN

**Objectives:** Polymorphisms in the cytochrome P-450 2D6 (CYP2D6) enzyme can affect antidepressant medication metabolism and blood levels. Approximately 8% of Caucasians of European descendants are 2D6 poor metabolizers (PM). There are numerous case reports of medication adverse outcomes with PM. In an inpatient mood disorders unit, we investigate the clinical differences between 2D6 PM and extensive (normal type) metabolizers (EM).

**Methods:** A retrospective chart review from January 2010 to November 2011 of patients hospitalized for unipolar or bipolar depression. The attending psychiatrist obtained genotyping in cases where it was thought helpful for medication selection, typically in patients who experienced more than usual side effects from medications or non-response to medications. Patients with 2D6 PM were compared to age and gender matched pairs of patients with 2D6 EM using univariate McNemar's test for these clinical characteristics: depression severity measured by PHQ-9 and HamD, previous medication and ECT trials, admission number of psychotropic medications, past hospitalizations, more than usual side effects to antidepressants, unipolar versus bipolar diagnoses, Cluster B personality traits, substance use, and whether the results changed the recommended treatment medications.

**Results:** Of 1121 patients, 329 (29%) were genotyped, identifying 41 2D6 PM. When compared to the paired group of 41 EM, the only clinical characteristics which were statistically different were (1) patients with PM had more psychotropic medications on admission (mean 3.6 vs 2.7, p=0.04) and (2) identification of PM resulted in treatment medications being changed (p=0.0006).

**Conclusions:** In our depressed inpatients, 2D6 PMs were clinically similar to 2D6 EMs, even in patient who reported more side effects with antidepressants. One significant difference is that patients with PM took more psychotropic medications, suggesting that might be a useful clinical variable in trying to identify PM. When patients were identified as PM, clinicians tended to change medications instead of continuing the same medications prior to genotyping. Whether those medication changes resulted in clinical patient improvement is beyond the scope of this study, but is an important area of future research.

**Learning Objectives:**
- To understand implications of 2D6 polymorphisms.
- To describe the clinical similarities and differences in hospitalized depressed patients who are poor vs normal 2D6 metabolizers.

**Source Of Funding:** None

**Literature References:**
- Sistonen J, et al. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenet Genomics. 2007;17:93-101.
- D'Empaire I, et al. Antidepressant treatment and altered CYP2D6 activity: are pharmacokinetic variations clinically relevant? J Psychiatr Pract. 2011;17:330-9.

## PREDICTORS OF RESPONSE AND REMISSION DURING AN OPEN-LABEL 10-WEEK TRIAL WITH SELEGILINE TRANSDERMAL SYSTEM (STS)

Sungwon Jung, MD, PhD[1], Saeheon Jang, MD[1], Chiun Pae, MD, PhD[1], Prakash S. Masand, MD[1], Kimberly Blanchard Portland, PhD[2], Paul Mastoridis[2], Ashwin A. Patkar, MD[1]

[1]Duke University, Durham, NC, [2]Dey Pharma, LP, Basking Ridge, NJ

**Objective:** Patient and treatment characteristics that influence treatment response and remission in major depressive disorder (MDD) are of clinical interest. This post hoc analysis investigated clinical characteristics predictive of response and remission in a 10-week open ¨Clabel trial of selegiline transdermal system (STS).

**Method:** The data analyzed included 10 weeks of open-label treatment with 6 mg/24 hrs of STS in patients with MDD. This was the stabilization phase of a 52-week, placebo-controlled double-blind relapse prevention trial with STS. Response was defined as ¡Ý 50% reduction in Hamilton Depression Rating Scale (HAMD-17) score and remission was defined as HAMD-17 score of ¡Ü 10. Pretreatment demographics, illness course, treatment resistance and symptom domains were studied to identify predictors of response.

**Results:** 675 patients entered the trial. The response rate was 53.3% by the end of 10 weeks and remission rate was 47.1%. Dropout rate was 15.4%. Early response (within first 2 weeks of treatment) ($p<0.005$), retardation ( $p<0.05$), sexual difficulties ($p<0.005$) and hypnotic use ( $p<0.05$) were significant predictors of response. The same factors also significantly predicted remission. Subjects with atypical, melancholic or anxious features had comparable response and remission rates on STS to those without those features.

**Conclusions:** Early response was a strong predictor of end of treatment response and remission with STS. Retardation and sexual difficulties also predicted outcome with STS. Patients with atypical or melancholic features responded equally well. The results demonstrate patient characteristics that may be helpful for clinicians while treating patients with STS.

**Key words:** Selegiline transdermal system, major depressive disorder, predictors, relapse

**Learning Objectives:**
- To understand clinical characteristics that may predict response/remission with short term (10 week) treatment with selegiline transdermal system (STS) in patients with major depressive disorder
- To better understand the safety profile of STS

**Source Of Funding:** Dey Pharma, LP

**Literature References:**
- Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. J Clin Psychopharmacol. 2006 Dec;26(6):579-86.
- Patkar AA, Pae CU, Masand PS. Transdermal selegiline: the new generation of monoamine oxidase inhibitors. CNS Spectr. 2006 May;11(5):363-75.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## STATISTICAL EVALUATION OF THE POWER OF THE ARC SINE TEST AGAINST THE CMH TEST FOR STRATIFIED DATA FOR SMALLER PROPORTIONS

Hewa P. Saranadasa, BS, PhD, MS[1], Shawki Salem, BS, PhD, MS[2]

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The power of the Arc Sine test for testing population proportions of two treatments was assessed against the CMH test for stratified data. The significance level and power of the Arc Sine test was compared with the CMH test using a Monte Carlo Study. The results showed that the Arc Sine test compared favorably against the CMH test in terms of Type I error rate, as well as the power when the sample size is large. The results also showed that the Arc Sine test tends to have a greater power compared with the power of the CMH test when the sample size is relatively small and the incidence rate of the underline distribution is low.

The sample size formulas for testing stratified population proportions from both tests are also derived. The application of Arc Sine test to compare the incidence of Pulmonary Embolism (PE) between the combined sub populations within the Extended-Release Epidural Morphine (EREM) and the control group is also discussed.

**Keywords:** CMH; Arc Sine Approximation; Power Calculation; Monte Carlo Study;

**Learning Objectives:**

- To compare the power of the Arc Sine test against the CMH test when the incidence rates are low for Stratified Data.
- To derive the power functions and sample size formulars for the Arc Sine test and also for the CMH test for the Stratified Data
- To Apply the Arc Sine Test to a practicle problem in which the proportions of incidence were low.

**Source Of Funding:** None

**Literature References:**

- Cochran WG: Some methods for strengthening the common tests. Biometrics 1954; 10: 417-451.
- Mantel N, Haenszel W: Statistical aspects of the analysis of data from respective Studies of disease. Journal of the National Cancer Institute 1959; 22: 719-748.
- Walters DE: In defence of the arc sine approximation. The Statistician 1979; 28:219-222.
- Blackshear RH, Crosson KC. Reduction in Pulmonary Embolism after total joint Arthroplasty: The years of experience with Extended-release Epidural Morphine. Pain Practice 2010; 10(3): 235-44.

## TRANSLATIONAL EVALUATION OF JNJ-18038683, A SELECTIVE 5-HT7 RECEPTOR ANTAGONIST IN DEPRESSION

Jaskaran Singh, MD[1], Michelle Kramer, MD[2], Christine Dugovic, PhD[3], Nicholas Carruthers, PhD[3], De Boer Peter, PhD[4], Pascal Bonaventure, PhD[3], Timothy Lovenberg, PhD[3], Maurizio Fava, MD[5]

[1]Janssen R&D, Titusville, NJ, [2]Johnson and Johnson, Tokyo, Japan, [3]Janssen R&D, La Jolla, CA, [4]Janssen R&D, Beerse, Belgium, [5]Massachusetts General Hospital, Boston, MA

5-$HT_7$ receptor blockade has been shown to be effective in rodent models of depression and to increase the latency to REM sleep and decrease REM duration. JNJ-18038683 is a selective 5HT7 receptor antagonist. JNJ-18038683 displaced, with high affinity, specific [$^3$H]5-CT binding sites and produced a concentration dependent decrease of serotonin-stimulated adenylyl cyclase from rat and human 5-$HT_7$ receptors expressed in HEK-293 cells. In rodents, JNJ-18038683 increased the latency to REM sleep and decreased REM duration which is maintained with multiple administrations. The compound was effective in a behavioral model of helplessness such as the mouse tail suspension test. In healthy human volunteers, JNJ-18038683 was found to increase REM latency and to decrease REM sleep duration demonstrating that the effect of 5-$HT_7$ blockade on REM sleep translated from rodent to humans. Like in rats, JNJ-18038683 was also found to enhance REM sleep suppression induced by citalopram in humans, although a drug-drug interaction could not be ruled out. In a double blind, active- and placebo-controlled randomized clinical study in patients suffering from depression, neither treatment with pharmacologically active doses of JNJ-18038683 nor citalopram separated from placebo, indicating a failed study lacking assay sensitivity. A post hoc analyses using an enrichment window strategy, where all the efficacy data from sites with an implausibly high placebo response (MADRS ≤ 12 at endpoint) and from sites with no placebo response (<10% improvement: MADRS >=28) are censored, there was a clinically meaningful and statistically significant difference between JNJ-18038683 and placebo. The preclinical and clinical data are suggestive of antidepressant efficacy of JNJ-18038683 and required further studies to characterize its potential antidepressant efficacy.

**Learning Objectives:**

- Role of 5HT7 in sleep and depression
- Translational development of a new antidepressant
- Site based enrichment analyses

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## CROSSOVER STUDIES IN CLINICAL RESEARCH: EXPERIENCE WITH CARRYOVER EFFECTS

David A. Luckenbaugh, Carlos A. Zarate, MD

NIMH, Bethesda, MD

Crossover designs provide advantages over other studies including more efficient control groups and a reduced sample size. However, they introduce concerns which make them less common than standard parallel designs. Among the major concerns is the potential for carrying over changes from an initial phase to the next, thereby altering the response in the second phase. Methodologists have suggested longer periods between crossover phases in order to reduce these concerns.

Inpatients were randomly assigned to a single infusion of 0.5 mg/kg of ketamine or placebo in the first phase and later crossed over to the opposite infusion in the second phase. In study 1, drug free patients with Major Depression (MDD) received infusions one week apart. In study 2 and 3, patients with Bipolar Disorder (BD) received infusions two weeks apart while taking either lithium or valproic acid. Psychiatric professionals rated symptoms 60 minutes prior to each infusion and 40, 80, 120, and 230 minutes after infusion as well as after 1, 2, 3, and 7 days. The BD patients were also rated after 10 and 14 days. The Hamilton Rating Scale for Depression and Montgomery-Asberg Depression Rating Scale were primary measures. Patients and staff were blind to the drug received in each phase. Only patients meeting a pre-specified depression level at the end of the first phase were crossed over to the second.

Twenty-two MDD and 33 BD patients participated. These studies showed significant improvement in depression. In the MDD study, 6/11 (55%) patients who received ketamine in the first phase were too well to crossover to the second. Only 1/11 (9%) were too well to crossover after placebo. With the BD studies, an extra week was added between phases to minimize this problem. Subsequently, none (0/16) of the patients who received ketamine first missed being crossed over due to being too well and only 1/17 (6%) first phase placebo patients were too well to crossover.

Crossover studies with ketamine suggested that extending the time between phases from one to two weeks was effective in reducing the amount of carryover from the first phase. These findings suggest that a major concern with using crossover studies could be handled effectively with a relatively basic adjustment in research design. Use of crossover studies could make clinical trials faster and less expensive.

**Learning Objectives:**

- Illustrate that carryover effects can be managed by design considerations.
- Show that crossover trials have a place in clinical research.

**Source Of Funding:** NIMH, DIRP

**Literature References:**

- DiazGranados N, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch. Gen. Psychi. 2010; 67: 793-802.
- Zarate C, et al. A randomized trial of an NMDA antagonist in treatment resistant major depression. Arch. Gen. Psychi. 2006; 63: 856-864.

## GENETIC PREDICTORS OF RESPONSE TO ANTIDEPRESSANT TREATMENT IN GERIATRIC DEPRESSION USING GWAS: A PILOT STUDY

Helen Lavretsky, MD, MS, Ascia Askin, PhD, Stan Nelson, PhD

UCLA, Los Angeles, CA

**Background:** Geriatric depression is commonly associated with insufficient antidepressant response. It is important to understand the genetic basis of treatment resistance and preferential response to antidepressants with dopaminergic or sertonergic properties.

**Methods:** 20 older adults with major depression (age 60 and older) were randomized to receive 16 weeks of treatment with methylphenidate+ placebo, citalopram+placebo, citalopram+ methylphenidate. The doses of methylphenidate ranged between 10-30 mg per day; and citalopram dose ranged between 20-40 mg per day. Genome-wide transcriptional profiling was carried out peripheral blood mononuclear cell samples obtained at baseline and post-intervention. Microarrays were run on the Illumina platform, Human HT-12_V4, and quantile normalized.

**Results:** Among 20 subjects, 7 subjects failed to respond to treatment and 13 subjects were rapid responders. The expression of two genes in the dopamine and serotonin pathways, SNCA (2.18 higher; P=0.036) (alpha-synuclein gene implicated in Parkinson's disease (SNCA) that binds dopamine transporter and is involved in the regulation of dopamine release and transport), and CA1 (2.53 times higher; t=0.029)(Carbonic anhydrase is involved in respiratory function and interacts with serotonin pathways) was higher at baseline in nonresponders. Treatment with methylphenidate upregulated genes–G-protein coupled protein signaling pathway involved in cellular aging (GPR175) and glutamate receptor NMDA protein 1 (GRINA).

**Conclusions:** The present results suggest unique genetic signature in responders and non-responders to antidepressant treatment in the dopaminergic and serotonergic pathways that may allow prediction of individual treatment resistance. Treatment with methylphenidate resulted in upregulation of genes in the glutamatergic, and G-protein signaling pathways, also important for neuroplasticity and brain aging. Our results will need to be replicated in larger samples with the use of additional specific biomarkers of the identified pathways.

**Learning Objectives:**

- To discuss genetic predictors of treatment resistnce in geriatric depression
- To discuss differences in gene expression with dopaminergic or sertonergic treatment

**Source Of Funding:** 5R01MH077650;5K24MH086481

**Literature References:**

- Lavretsky, H., Kim, MD, Kumar, A. & Reynolds, C.F. (2003) Combined treatment with methylphenidate and citalopram for accelerated response in the elderly: an open trial. J. Clin. Psychiatry, 64, 1410–1414.
- Lavretsky H, Siddarth P, Wong M-L, Kumar A, Reynolds C. Dopamine and serotonin transporter genetic polymorphisms: clinical features and treatment response in geriatric depression Int Journal of Geriatric Psychiatry 2007 July 10: 1-5.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## CLINICAL TRIAL SITE EXPERIENCES & ATTITUDES TOWARDS PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR (SIB): RESULTS OF A GLOBAL INTERNET-BASED SURVEY

Adam Butler[1], Michelle Stewart, PhD[2], Larry Alphs, MD, PhD[3], Phil Chappell, MD,[2], Douglas Feltner, MD[4], William R. Lenderking, PhD[5], Atul Mahableshwarkar, MD[6], Clare Makumi, PharmD[7], Sarah DuBrava, MS[8]

[1]Bracket, Wayne, PA, [2]Pfizer, Inc., Groton, CT, [3]Janssen Pharmaceutical Companies, Titusville, NJ, [4]Douglas E. Feltner, LLC, Novi, MI, [5]United BioSource Corporation, Lexington, MA, [6]Takeda Global R & D, Deerfield, IL, [7]GlaxoSmithKline, Research Triangle Park, NC, [8]Pfizer, Inc, Groton, CT

**Introduction:** The International Society for CNS Clinical Trials and Methodology (ISCTM) Suicidal Ideation and Behavior Working Group conducted an online survey regarding clinical trial site experiences and attitudes towards suicidal ideation and behavior (SIB) data collection following the 2010 release of the FDA draft guidance on prospective assessment of SIB in clinical trials to support the classification of such events. The ISCTM Secretariat sent an email invitation with a link to the 20-item online survey to 6058 sites that had participated in at least one CNS clinical trial in the prior 2 years.

**Results:** 1004 responses were collected (43% US). Respondents included principal investigators (36%), raters (28%), coordinators (25%), and others (11%). The majority (80%) had conducted SIB assessments. Majority were psychiatrists (43%) and reported using SIB assessments across many indications. Overall, respondents indicated that prospective assessment is ~~-w~~orth the additional burden" (73%), has been ~~-ea~~sy to incorporate" (73%) and has ~~-im~~proved subject safety" (74%). The greatest challenge was getting accurate baseline lifetime history (54%), while the greatest benefit was identifying subjects at risk of suicide (85%). Approximately a quarter of respondents reported implementation challenges such as training issues. Differences based on geographical region, respondent's role and responsibility for assessments were observed. Open-ended responses revealed additional challenges, e.g., use in cognitively impaired populations.

**Conclusion:** Prospective SIB monitoring was generally viewed positively though specific challenges were identified. Study limitations include self-report survey methodology and recruitment of sites based on CNS trial experience. These findings may help guide stakeholders' use of SIB assessments in clinical trials.

**Learning Objectives:**

- Provide overview of benefits and challenges from clinical trial site perspective of implementing SIB assessment in CNS clinical trials.
- Identify regional and sub-group differences that may guide future use of these assessments.

**Source Of Funding:** ISCTM supported the implementation of the survey with staff time and funding.

**Literature References:**

- Suicidality: Prospective Assessment of Occurrence in Clinical Trials; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf; accessed December 21, 2011.
- Posner K., Oquendo MA, Gould M., Stanley B., Davies G.: Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007; 164:1035-1043.

## 7 DEADLY SINS: GUIDELINES FOR REPORTING CLINICAL TRIAL METHODOLOGY RESEARCH

Danielle Popp, PhD[1], Janet B.W. Williams, PhD[1,2], Michael J. Detke, MD, PhD[1,3]

[1]MedAvante, Inc., Hamilton, NJ, [2]Department of Psychiatry, Columbia University, New York, NY, [3]Indiana University School of Medicine, Indianapolis, IN

**Background:** Clinical trial failure rates in several disease areas are about 50%. Many methodological approaches for increasing signal detection have been proposed but reporting variations deter comparisons. Standardization will alleviate this and reduce reporting bias in studies evaluating clinical trial methodology (CTM).

**Methods:** We propose 7 guidelines for standardized reporting and illustrate how misuse or omission influences interpretation of results.

**Results:** Report interrater reliability (IRR). IRR should be reported in studies with multiple raters and observations. For severity assessments, the ICC is required to accurately assess IRR. If individual items from a single severity scale are treated as separate observations, ICCs may be inversely related to IRR.

Use appropriate statistical tests. Kappa does not capture concordance on continuous variables. Using a fixed criterion to indicate rater agreement with a ~~-g~~old standard" score can inflate reports of IRR.

Include effect size measures. Measures of effect size should be reported regardless of statistical significance to allow readers to determine clinical relevance, regardless of sample size, and compare both within and across studies.

Identify a priori and post-hoc analyses. Methodological comparisons should be identified a priori or reported as post-hoc. Failure to do so can lead to over-interpretation of exploratory analyses performed on small subsets of data.

Acknowledge and correct for multiple comparisons. All analyses should be reported if multiple comparisons are performed on a single sample. Reporting a significant result on a subset of data without indicating total comparisons made across the entire data set or correcting for multiplicity may lead to over-interpretation of false positives.

Include inferential statistics for means comparisons. Statements concerning differences or patterns in means should be substantiated with inferential statistics.

Correct interpretation of null hypothesis testing (NHT). NHT is commonly misinterpreted, such as concluding that smaller p values indicate more important effects, or that a non-significant p value represents a finding of no difference.

**Conclusions:** Guidelines for standardized reporting of methodology research may reduce reporting bias. Empirical research evaluating effectiveness of new methods to increase signal detection holds important consequences for CTM.

**Learning Objectives:**

- Understand importance of standardized reporting
- Identify information necessary to compare results across methodologies

**Source Of Funding:** MedAvante, Inc.

**Literature References:**

- Schulz KF, Altma DG, Moher D, CONSORT Group: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. J Pharmacol Pharmacother 2010; 1:100-107.
- Muller MJ, Szegedi, A: Effect of interrater reliability of psychopathologic assessment on power and sample size calculations in clinical trials. J Clin Psychopharm 2002; 22:318-325.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## VILAZODONE IS NOT A SUBSTRATE BUT MAY BE A WEAK INHIBITOR OF P-GLYCOPROTEIN

Haijian (Jim) Zhu, PhD[1], Venugopal P. Marasanapalle, PhD[1], Patricia Gonzalez, MS[1], Muhammad Ahasan, BS[1], Haodan Yuan[1], Daksha Desai-Krieger[1], Ramesh Boinpally, PhD[1], Tobie Escher, PhD[2], Andreas Grill, BS[1], Fuxing Tang, PhD[1]

[1]Forest Research Institute, Farmingdale, NY, [2]Forest Research Institute, Jersey City, NJ

**Objective:** P-glycoprotein (P-gp), a drug transporter expressed in gut and brain, can efflux a wide variety of structurally and pharmacologically diverse compounds from the cell. Some antidepressant drugs (such as citalopram, venlafaxine, sertraline, paroxetine, fluoxetine, fluvoxamine, and reboxetine) are substrates or inhibitors of P-gp; this can alter absorption kinetics, reduce penetration into the brain (the site of antidepressant action), and alter the pharmacokinetics of concomitantly administered medications. Vilazodone is a serotonin reuptake inhibitor and 5-$HT_{1a}$ receptor partial agonist approved for the treatment of adult major depressive disorder. We evaluated the activity of vilazodone as a P-gp substrate and as an inhibitor.

**Methods:** Transport experiments were conducted through cell monolayers in both apical-to-basolateral (A→B) and B→A directions using the Caco-2 cell model. Cell monolayer integrity was checked using transepithelial electrical resistance and the low permeability molecule [$^{14}$C]-mannitol. Efflux of [$^{3}$H]-digoxin, a strong P-gp substrate, was tested in the presence and absence of the P-gp inhibitor cyclosporine A (CysA, 25 μm) to validate P-gp activity. Vilazodone was tested at concentrations of 0.3, 1, and 3 μg/ml; these concentrations are higher than the Cmax values at the clinical dose of 40 mg. An apparent permeability ($P_{app}$) ratio [$P_{app}$B→A/ $P_{app}$A→B] was used to determine polarized efflux; a ratio of ≥2 indicated significant P-gp substrate activity. P-gp inhibitory activity of vilazodone was evaluated by determining its effects on P-gp–mediated efflux of [$^{3}$H]-digoxin.

**Results:** Cell layer integrity was confirmed by electrical resistance >250 Ω-cm$^2$ and [$^{14}$C]-mannitol permeability of less than 1x10$^{-6}$ cm/sec with a $P_{app}$B→A/ $P_{app}$A→B ratio of 1.14. $P_{app}$B→A/ $P_{app}$A→B ratio for [$^{3}$H]-digoxin was 10.06, verifying P-gp activity; the addition of CysA decreased the ratio to 1.16. Vilazodone showed high permeability with values >24x10$^{-6}$ cm/sec. Vilazodone concentrations of 0.269-2.358 μg/ml showed a $P_{app}$B→A/ $P_{app}$A→B ratio ≤2, indicating that it is not a P-gp substrate; the addition of CysA did not affect the ratio. Low vilazodone concentrations (0.05-0.275 μg/mL) did not affect the [$^{3}$H]-digoxin permeability ratio, which was ~8.5, indicating minimal inhibitory effects. The ratio dropped dose-dependently with vilazodone concentrations of 0.55-22 μg/mL (ratios 7.04-2.25). The $IC_{50}$ value was 2.685; the [I]/$IC_{50}$ for vilazodone at 40 mg/day (recommended dose) was 0.024 (fasted) and 0.063 (fed), which is below the 0.1 threshold that establishes a drug as a P-gp inhibitor. Correcting for concentration in the GI tract predicts that vilazodone may be a weak P-gp inhibitor in GI compartments.

**Conclusion:** Vilazodone is a high permeability molecule that is not a substrate for P-gp. Vilazodone shows minimal inhibitory effects and no clinically significant role for P-gp is expected in the pharmacokinetics of vilazodone.

**Learning Objectives:**

- At the conclusion of the presentation, participants should be able to evaluate whether vilazodone is a P-gp substrate.
- At the conclusion of the presentation, participants should be able to evaluate the inhibitory effects of vilazodone on P-gp.

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

**Literature References:**

- Khan A: 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.
- O'Brien FE, Dinan TG, Griffin BT, Cryan JF: Interactions between antidepressants and P-glycoprotein at the blood-brain barrier: clinical significance of in vitro and in vivo findings. Br J Pharmacol 2012; 165(2):289-312.
- Weiss J, Dormann SM, Martin-Facklam M, Kerpen CJ, Ketabi-Kiyanvash N, Haefeli WE: Inhibition of P-glycoprotein by newer antidepressants. J Pharmacol Exp Ther 2003; 305(1):197-204.

## GENDER CONTRASTS AND SIMILARITIES IN NEURAL UNDERPINNINGS OF EATING BEHAVIOR AND BMI

Lawrence A. Maayan, BS, MD[1,2], Allison S. Larr, BS[1], Melissa M. Benedict, BS, MS[1], Alexis L. Moreno, BS, LSW[1], Laura J. Panek, BS[1], Jay Nierenberg, BS, MD, PhD[1,2], Matthew J. Hoptman, BS, PhD[1,2], Daniel C. Javitt, BS, MD, PhD[1,3], Francisco X. Castellanos, BS, MD, MS[1,2], Michael P. Milham, BS, MD, PhD[1], Bennett L. Leventhal, BS, MD[1,2]

[1]Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, [2]New York University Medical Center, New York, NY, [3]Columbia University, New York, NY

**Objective:** To elucidate gender differences and similarities in resting state fMRI co-activation correlated with eating behavior and obesity in a large community sample.

**Methods:** As part of a larger data-sharing initiative 44 women and 57 men fasted 8 hours before selecting breakfast items from a standardized array, later completing a 10-minute resting state fMRI scan on a Siemens 3T Magnetom scanner. All images were preprocessed using Functional Connectomes Project scripts and processed using mixed-effects analyses implemented in FSL and AFNI 9 seed-regions were selected for their relationship with reward and response inhibition. Cluster-based Gaussian random field corrected threshold Z-level was 2.3 and p was 0.05.

**Results:** As BMI increased pre- [(18.3, 35.9, 46.2), p = 0.0039) and post-central gyrus [(43.3, 34.2, 44.3), p = 0.00143) showed decreasing co-activation with bilateral nucleus accumbens seeds across all subjects, and with right nucleus accumbens in males and left nucleus accumbens in females. Left orbitofrontal cortex (LOFC) showed increasing coactivation with insula and precentral gyrus [(14.7, 43.9, 28.5), p = 0.0086] bilaterally in all subjects and right insula[(15.4, 43.5, 27.2), p = 0.00499] alone in women. Overall, individuals who ate more fat in the test meal had less coactivation between both nuclei accumbens seeds and left inferior frontal gyrus [(42.4, 48.1, 23.3), 614, p = 0.000273] while in males only the left nucleus accumbens seed had a decreasing coactivation with both inferior frontal gyri. Women and men who ate more fat in the test meal had significantly different coactivations to medial frontal gyrus [(29.7, 56.6, 22.9), p = 0.000101] from left and right insula as well as anterior cingulate. As BMI increased they also had different coactivation between middle frontal gyrus[(41.3, 57.3, 28.6), p = 0.00524] and left nucleus accumbens.

**Discussion:** This is the largest analysis of resting state functional connectivity with BMI and eating behavior to date. Frontal areas often associated with executive function had different coactivations with reward regions between men and women as BMI increased and as proportion of fat eaten increased. Individuals who ate more fat in the test meal had less of an association between reward specific areas (nuclei accumbens) and inhibitory areas (inferior frontal gyri). For BMI, lower weight individuals showed increased co-activation between areas of taste and motor cortex (pre and post-central gyri) and reward areas, echoing previous work showing higher activations in somato-sensory cortex to visual food cues in lean rather than obese. Findings from the left orbito-frontal cortex show an increasing coactivation between areas that evaluate reward (LOFC) and gustatory cortex as BMI increases. As previous work has suggested evidence for both increased and decreased reward sensitivity in obese as opposed to lean individuals, this study shows the utility of resting state functional connectivity and the power of large data sets to delineate the subtleties of these relationships. Further study of these relationships will assist in the understanding and treatment of obesity, eating disorders and disordered eating due to psychiatric medications and disorders.

**Learning Objectives:**

- Understand similarities and differences between men and women in neural underpinnings of obesity and eating behavior
- Learn about application of resting state functional connectivity to questions of weight.
- Consider issues in reward sensitivity and its relationship to obesity
- Understand contrasts in executive function and its relationship to eating behavior in women and men

**Source Of Funding:** New York State OMH, NIMH

**Literature References:**

- NKI/Rockland Sample. International Neuroimaging Datasharing Initiative (INDI), http://fcon_1000.projects.nitrc.org/indi/pro/nki.html.
- M.W. Woolrich, et al, Bayesian analysis of neuroimaging data in FSL. NeuroImage, 45:S173-186, 2009.
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**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## BAYESIAN PREDICTIVE POWER FOR ADAPTIVE DESIGNS

Cynthia Siu, PhD[1], Carla Brambilla, MS[2], Fabrizio Ruggeri, PhD[2]

[1]Data Power (DP), Inc., Ringoes, NJ, [2]IMATI, Milano, Italy

**Objective:** This paper presents an adaptive design method that uses Bayesian tools to build flexible clinical trial designs with good operating characteristics, controlled Type 1 and Type II error rates with adequate statistical power (eg. > 80%). The method produces a stopping boundary to monitor emerging results in a clinical trial for effectiveness while allowing early stopping for futility when there is little evidence of a beneficial effect.

**Methods:** To illustrate the adaptive design method, we modify the usual O'Brien-Fleming type boundary (designed for monitoring effectiveness) to include a futility analysis at 50% enrollment, based on Bayesian predictive power. Results (Z-statistics) from sequential interim analysis can be combined using weighted-Z method.

**Results:** We defined trial success as obtaining statistically significant treatment effect, i.e. test statistics Z < 1.96 under the null hypothesis of no treatment effect. For studies designed with 85% power and 5% Type-I error, we calculated the futility decision boundary. At information time 0.5 (50% of planned enrollment), the trial is stopped for futility if Bayesian predictive power < 25% (probability of trial success). This yields final Z-test critical value P<0.0596 and total Type-2 error rate 18%. We can also calculate the stopping boundary values for monitoring early benefits (4 interim analyses) while allowing the trial to stop for futility (1 futility analysis at 50% enrollment), this yields the total Type-I error rate 0.051 and power 82%.

**Conclusions:** These results show Bayesian predictive power is a useful tool to build flexible adaptive designs that have acceptable operating characteristics for randomized clinical trials. The method described here is versatile and hence applicable to a rich family of adaptive design and sequential analysis strategies.

**Learning Objectives:**
- To further understanding of Bayesian predictive power for adaptive designs
- To better understand the usual frequentist interim analysis method and the Bayesian approach

**Source Of Funding:** Data Power (DP), Inc.

**Literature References:**
- Lan KKG; Soo Y; Siu C; Wang M: The use of weighted Z-tests in medical research. J of Biopharmaceutical Statistics 2005; 15:625-639.
- Fisher LD: Self-designing clinical trials. Statistics in Medicine 1998; 17:1551-1562.

## 5 URBAN LEGENDS OF CNS CLINICAL TRIAL METHODOLOGY: UNSUCCESSFUL SOLUTIONS TO THE PROBLEM OF FAILED TRIALS

Janet B.W. Williams, PhD[1,2], Danielle Popp, PhD[1], Scott Reines, MD, PhD[1], Michael J. Detke, MD, PhD[1,3]

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**Introduction:** As the rate of failed trials in CNS has grown, drug developers have attempted strategies to improve signal detection and reduce failures. We present 5 common strategies and evaluate their effectiveness.

**Methods:** 1. Increasing sample. If statistical power increases with sample size and effect size is fixed, it appears reasonable that increasing sample size will increase effect size. Liu et al. examined 4 depression trials to evaluate this theory.

2. Choosing ~~p~~roven" sites. Some believe that selecting sites with proven effectiveness across several studies will continue to yield positive results. Gelwicks et al. analyzed data from sites that participated in at least 2 trials with at least 30 subjects.

3. Using experienced raters. It seems logical that more experienced raters will minimize variability and improve signal detection. Kobak et al. examined interrater agreement across 3 cohorts of raters: experienced and calibrated, experienced but non-calibrated, and inexperienced.

4. Increasing training. Variability across raters in a trial negatively affects study power and signal detection. To reduce variability, Demitrack et al. trained raters in an intensive session with videotapes and discussion.

5. Using certain regions. Many believe greater signal detection can be obtained outside the US. Khin et al. conducted a meta-analysis of FDA data on 81 US and ex-US antidepressant trials.

**Results:** 1. Increasing sample. In 3 positive studies, treatment effect was observed before the first 100 subjects per treatment arm were enrolled. Treatment effect size decreased over time despite increases in sample size.

2. Choosing ~~p~~roven" sites. Site performance across consecutive studies was inconsistent (all correlations <.50).

3. Using experienced raters. Calibration appears to improve reliability over and above experience alone. Experienced and calibrated raters had the highest ICC (.93) whereas experienced and non-calibrated raters had the lowest ICC (.55).

4. Increasing training. ICCs did not improve across 6 hours of training.

5. Using certain regions. Analysis revealed increasing placebo response across US and ex-US regions, and a similar decrease in US and ex-US effect size.

**Conclusion:** Strategies for improving signal detection are often used, despite a lack of clear evidence of their effectiveness. These ~~ur~~ban legends" are widely touted, but evidence to support them is mixed at best.

**Learning Objectives:**
- Understand methods used to improve signal detection
- See reasons why some are ineffective

**Source Of Funding:** MedAvante, Inc.

**Literature References:**
- Kobak KA, Brown B, Sharp I, Levy-Mack H, Wells K, Ockun F, Williams JBW. Sources of unreliability in depression ratings. J Clin Psychopharm 2009; 29 (1),82-85.
- Liu KS, Snavely DB, Ball WA, Lines CR, Reines SA, Potter WZ. Is bigger better for depression trials?.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## PALIPERIDONE PALMITATE (PP) FOR MAINTENANCE TREATMENT OF SCHIZOAFFECTIVE DISORDER (SCA): BASELINE DATA

Dong-Jing Fu, MD, PhD[1], Ibrahim Turkoz, MS[2], Richard B. Simonson, BS[2], David Walling, PhD[3], Nina Schooler, PhD[4], Jean-Pierre Lindenmayer, MD[5], Larry Alphs, MD, PhD[1]

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**Background:** Baseline data of subjects enrolled in the first ongoing maintenance study of PP, a long-acting injectable antipsychotic, for treatment of SCA are presented.

**Method:** This randomized, double-blind (DB), placebo (PBO)–controlled international study (NCT01193153) includes subjects with SCID-confirmed DSM-IV diagnosis of SCA in acute symptomatic exacerbation defined by score >=4 on >=3 PANSS items corresponding to SCA symptoms and prominent mood symptoms (YMRS and/or HAM-D-21>=16). Subjects may receive concomitant treatment with stable antidepressant (AD) or mood stabilizer (MS) doses. After stabilization with PP (78–234 mg/mo) during a 13-week, flexible-dose period, stable subjects (PANSS total<=70, YMRS<=12, and HAM-D-21<=12) continue to the 12-week open-label (OL) fixed-dose period. Those who meet stabilization criteria are randomized (1:1) to PP or PBO in the 15-month DB period. Primary endpoint: first occurrence of relapse.

**Results:** As of 11/25/2011, 491 subjects entered the OL period. Mean age (range): 40.0 (19–64) years. 52.3% were male. Mean age (range) at first psychiatric and SCA diagnoses: 25.9 (3–55) and 31.3 (7–59) years, respectively. 27.6% had a suicide attempt history. Mean prior lifetime psychiatric hospitalizations (range): 6.2 (0–150). 55.4% were taking concomitant AD or MS. Mean (SD) baseline scores: PANSS total, 85.7 (12.9); HAM-D-21, 20.9 (7.7); YMRS, 18.0 (9.4).

**Conclusions:** Study sample highlights well-known SCA characteristics: full range of psychotic and mood symptoms, repeated prior hospitalizations, high suicide attempt rate and combination treatments, and late diagnosis identification. Results should be broadly generalizable to SCA subjects.

**Learning Objectives:**

- To educate participants on characteristics of schizoaffective disorder
- To educate participants on the ongoing clinical study of paliperidone palmitate for maintenance treatment of schizoaffective disorder

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

**Literature References:**

- Canuso C.M., Turkoz I., Fu D.J., Bossie C.A. Role of paliperidone extended-release in treatment of schizoaffective disorder. Neuropsychiatr Dis Treat 2010; 6:667-679.
- Hough D., Gopal S., Vijapurkar U., Lim P., Morozova M., Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr Res 2010; 116:107-117.

## PATTERNS OF MEDICATION ADHERENCE AND RESOURCE UTILIZATION AMONG PATIENTS WITH SCHIZOAFFECTIVE DISORDER (SCA)

Michael Markowitz, MD[1], Sudeep Karve, PhD[2], Dong-Jing Fu, MD, PhD[1], Jean-Pierre Lindenmayer, MD[3], Chi-Chuan Wang, PhD[2], Sean D. Candrilli, PhD[2], Larry Alphs, MD, PhD[1]

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**Introduction:** To assess patterns of medication adherence and resource utilization and costs during clinically relevant periods of pre–hospital admission (60-day intervals, over 6 months) and post–hospital discharge (60-day intervals, over 12 months) in patients with SCA.

**Methods:** A retrospective cohort analysis of the MarketScan Medicaid database (2004-2008) was conducted. Medication (antipsychotic, antidepressant, and mood stabilizer) adherence (proportion of days covered) and all-cause and SCA-related resource utilization and costs were assessed among hospital-discharged SCA patients during preadmission and postdischarge periods. Outcomes were compared between each adjacent 60-day postdischarge period using univariate and multivariable analyses.

**Results:** Among the selected 1193 patients (39% male; 43% black), adherence rates declined in the preadmission periods (180-121 days: 65%; 120-61 days: 49%; 60-0 days: 46%) and increased in the initial 60-day postdischarge period (80%). SCA-related total costs were significantly greater in the initial 0-60 day (mean: $2370 vs $1765; P<0.001) postdischarge period compared with the 61-120 day period, with rehospitalization (mean: $860 vs $483) and pharmacy (mean: $954 vs $758) being the primary drivers of higher costs in the 0-60 day period.

**Conclusion:** The medication adherence and resource utilization patterns presented in our study should help identify high-risk patients and may help physicians tailor treatment strategies to lower the direct and indirect economic burden in patients with SCA.

**Learning Objectives:**

- To highlight the concept that hospital-discharged patients with SCA have a high likelihood of rehospitalization
- To illustrate patterns of psychotropic medication adherence and of resource utilization and costs across various care settings (eg, inpatient, outpatient) during pre–hospital admission and post–hospital discharge periods among SCA patients

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

**Literature References:**

- Doering S., Müller E., Köpcke W., Pietzcker A., Gaebel W., Linden M., Müller P., Müller-Spahn F., Tegeler J., Schüssler G. Predictors of relapse and rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Bull 1998; 24(1):87-98.
- Thompson E.E., Neighbors H.W., Munday C., Trierweiler S. Length of stay, referral to aftercare, and rehospitalization among psychiatric inpatients. Psychiatr Serv 2003 Sep; 54(9):1271-1276.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## THE INCIDENCE OF TARDIVE DYSKINESIA IN THE STUDY OF PHARMACOTHERAPY FOR PSYCHOTIC DEPRESSION (STOP-PD)

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**Introduction:** Major depression with psychotic features (MDpsy) is a severe form of major depressive disorder (MDD) that carries significant morbidity and a poor prognosis. The use of antipsychotics in patients with mood disorders has been associated with an elevated risk of developing tardive dyskinesia (TD) with a shorter duration of treatment and lower cumulative dose of antipsychotic than in patients with schizophrenia. Older age has also been associated with higher incidence of TD with antipsychotic treatment. Most data on the risk for TD pertains to younger patients with schizophrenia or older patients with dementia who may have a different risk and, typically, are exposed to antipsychotics for longer durations. Case identification rates using rating scale criteria vary widely and the incidence of rating scale indentified-TD in this trial (4.3%) far exceeded the number of participants with a clinically adverse event (0.4%). Because of this disparity and the expectation that different criteria for capturing TD would result in different frequency rates, we applied different criteria sets to estimate a range for the baseline prevalence and incidence during short-term exposure in younger and older patients with MDPsy who participated in a 12-week clinical trial comparing olanzapine plus sertraline vs. olanzapine plus placebo.

**Methods:** All subjects (N = 259) were assessed with the Abnormal Involuntary Movement Scale (AIMS) at baseline, and after 4, 8, and 12 weeks of treatment. We used seven different operationalized criteria (Schooler-Kane, Persistent Schooler-Kane, Modified Schooler-Kane, Glazer-Morgenstern, Global AIMS rating, Operationalized Global rating, Adverse Event Data) to estimate the prevalence of TD at baseline and the incidence over the duration of the trial. For each set of criteria, we determined which subjects met criteria for TD at baseline. These subjects were excluded from further analysis and we then applied the criteria to the other subjects to assess the incidence of TD during the study. Finally, using each set of criteria, we compared the prevalence of TD at baseline and the incidence of new cases in patients younger or older than 60 years old using a Fisher's exact test.

**Results:** The overall prevalence and incidence of TD varied almost six-fold depending on the criteria used (prevalence range: 1.2% to 8.9%; incidence range: 0.0% and 5.9%). TD was observed as a clinical adverse event in only one subject (0.4%). Older subjects had a much higher prevalence of TD at baseline compared to younger adults(2.1% to 13.4% vs. 0.0% to 3.4%). However, the incidence in younger and older subjects did not differ significantly on any of the criteria.

**Conclusion:** To our knowledge this is the first large, randomized-controlled study to report the incidence of TD in a sample of subjects with MDpsy treated with an atypical antipsychotic. The incidence of TD was relatively low in both younger and older patients with MD-Psy treated acutely with olanzapine. The results demonstrate that the clinically meaningful emergence of TD occurs in less than one percent of MDpsy patients across the lifespan treated with Olanzapine over a 12-week period. Our results also highlight the need for greater consistency in measuring the emergence of TD in trials of patients being treated with antipsychotic for indications other than schizophrenia, as the incidence rates varied 6 fold depending on the criteria used.

**Learning Objectives:**

- To appreciate the different criteria for diagnosing tardive dyskinesia
- To appreciate that rates of Tardive Dyskinesia can very widely depending on the criteria used to make the diagnosis

**Source Of Funding:** Supported by USPHS grants MH 62446, MH 62518, MH 62565, MH 62624, MH069430 and MH 086686 from the National Institute of Mental Health and by a fellowship from the Canadian Institutes of Health Research - Institute of Aging (DMB).

**Literature References:**

- Rothschild AJ. Challenges in the treatment of depression with psychotic features. Biol Psychiatry 2003;53:680-90.
- Kane JM. Tardive dyskinesia in affective disorders. J Clin Psychiatry 1999;60 Suppl 5:43-7; discussion 8-9.
- Jeste DV. Tardive dyskinesia rates with atypical antipsychotics in older adults. J Clin Psychiatry 2004;65 Suppl 9:21-4.
- Nelson JP, GI. Antipsychotic drugs for depression? Am J Psychiatry 2010;167:216; author reply -9.

## DEVELOPMENT OF A RULE SWITCHING TEST DESIGNED TO ASSESS EXECUTIVE CONTROL

Keith A. Wesnes, PhD[1,2], Chris Edgar, PhD[3], Richard Wojciak[1], Howard Hassman, PhD[4], Maria Pinho[4], David Kreftez, MD[4], Daniel Gruener, MD[4], Lawrence Brownstein[4], Jean Dries[5]

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**Background:** Executive function is a set of cognitive abilities that control and regulate other aspects of function to facilitate goal-directed behaviour. One experimental paradigm for assessing aspects of executive control is requiring subjects to switch between two tasks. We evaluated a test in which such switching has previously been shown to involve activation of the medial and dorsolateral areas of the frontal cortex (DiGirolamo GJ et al, 2010).

**Methods:** In this rule switching test (RST), strings of identical digits of varying length are presented on a computer screen (eg 888, 111111, 3333). In one condition, the subject has to determine whether the number of digits in each string is greater or smaller than 5, and in another condition whether the value of the digits is greater or smaller than 5. There are never 5 digits in the string and the digit 5 is not used. Each condition is associated with a particular colour which is presented before each string. The subject initially performs each condition separately in a block of 36 trials. Then in the ‗switching' phase, the subject is required to apply the rule according to the colour presented prior to each successive string; the colors being presented in an unpredictable sequence, forcing the subject to decide which rule to apply trial by trial. In the present study, 41 healthy volunteers aged 21 to 55 years performed the RST on three study days alongside Parts A and B of the trail making test (TMT). Part A of the TMT involves a single rule, while Part B involves rule switching. Analysis of variance was used to compare the performance between the various phases of the RST and correlations were run to establish test-retest reliability and examine relationships between the two tests and performance with the age of the volunteers. Further studies using the same methodology are underway using schizophrenic and bipolar patients.

**Results:** In the RST, the subjects took significantly longer to respond in the switching phase than when performing the task using either one of the rules ($p<0.001$), this performance change reflecting the demands of rule switching and providing an assessment of executive control. The test-retest reliability of the speed scores in the switching and nonswitching conditions of the RST was good (r=0.58 to 0.89), as was that for Parts A and B of the TMT (r=0.60 to 0.87). There were also statistically significant correlations between the RST switching condition and Part B of the TMT ($r=0.37$, $p<0.02$), as well as between the extra response time in the switching condition of the RST and the longer completion time of the TMT Part B ($r=0.32$, $p<0.05$). Further, the extra response time in the switching condition of the RST correlated with the age of the volunteers ($r=0.5$, $p<0.001$), indicating that the test is sensitive to age-related declines.
DISCUSSION: The RST appears to be suitable for repeatedly assessing executive control over time in clinical trials with volunteers. Early readouts of the data from follow up trials with schizophrenic and bipolar patients will be presented.

**Learning Objectives:**

- To appreciate how tests can be designed to assess aspects of executive function
- To understand the process of task validation for clinical trials

**Source Of Funding:** Bracket Global

**Literature References:**

- DiGirolamo GJ et al. General and task-specific frontal lobe recruitment in older adults during executive processes: A fMRI investigation of task-switching. NeuroReport 2010, 12: 2065-2071.
- Saxby BK et al. Effects of Hypertension on attention, memory and executive function in older adults. Health Psychology 2003. 22: 587-591.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## CONVERGENT FUNCTIONAL GENOMICS OF SCHIZOPHRENIA: FROM COMPREHENSIVE UNDERSTANDING TO GENETIC RISK PREDICTION

Alexander B. Niculescu, MD, PhD

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We have used a translational convergent functional genomics (CFG) approach to identify and prioritize genes involved in schizophrenia, by gene-level integration of genome-wide association study (GWAS) data with other genetic and gene expression studies in humans and animal models. Using this polyevidence scoring and pathway analyses, we identify top genes, brain development, myelination, cell adhesion, synaptic long term potentiation, and glutamate receptor signalling as key to pathophysiology and as targets for therapeutic intervention. Overall, the data is consistent with a model of disrupted connectivity in schizophrenia, resulting from the effects of neurodevelopmental environmental stress on a background of genetic vulnerability. In addition, we show how the top candidate genes identified by CFG can be used to generate a polygenic risk prediction score to aid schizophrenia diagnostics . We also show, in three independent cohorts, two European-American (EA) and one African-American (AA), increasing overlap, reproducibility and consistency of findings from SNPs to genes, then genes prioritized by CFG, and ultimately at the level of biological pathways and mechanisms. Lastly, we compared our top candidate genes for schizophrenia from this analysis with top candidate genes for bipolar disorder and anxiety disorders from previous CFG analyses conducted by us, as well as findings from the fields of autism and Alzheimer. Overall, our work maps the genomic and biological landscape for schizophrenia, providing leads towards a better understanding of illness, diagnostics, and therapeutics. It also reveals the significant genetic overlap with other major psychiatric disorder domains, sugesting the need for improved nosology.

**Learning Objectives:**
- Genetics of schziophrenia
- Genetic testing
- Biomarkers
- New targets for drug development

**Source Of Funding:** This work was supported by an NIH Directors' New Innovator Award (1DP2OD007363) and a VA Merit Award (1I01CX000139-01) to ABN.

**Literature References:**
- Le-Niculescu, H. et al. Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics). 2007; 144B (2):129-158.
- Kurian, S. M. et al. Identification of Blood Biomarkers For Psychosis Using Convergent Functional Genomics. Molecular Psychiatry 2011;16(1):37-58. Epub 2009 November 24.
- Niculescu AB, et al. Convergent Functional Genomics: What we have learned and can learn about genes, pathways and mechanisms. Neuropsychopharmacology 2010. 35(1):355-6.
- Purcell, S. M. et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 2009; 460, 748-752.

## RP 5063 SAFETY, PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) IN SCHIZOPHRENIA

Marc Cantillon, MD, Sarath Kanekal, PhD, Mike Li, PhD, Grace Li, PhD, Robert Ings, PhD, Kouacou Adiey, PhD, Laxminaran Bhat, PhD

Reviva, San Jose, CA

**Background:** RP5063, a new atypical antipsychotic with partial agonist activity at D2, partial agonist activity at 5-HT1A, and antagonist activity at 5-HT2A receptors is a Dopamine-Serotonin System Stabilizer being developed for treating schizophrenia. It has high affinity to D2S, D2L, D3, D4.4, 5-HT1A, 5-HT2A, 5-HT26, and H1 receptors.It has moderate affinity for α 1B, D1, D5, 5-HT7, and SERT receptors with no significant affinity for 5-HT3, 5-HT1B, H3, M3, AChE and NMDA receptors. RP5063 has no cardiovascular, pulmonary or CNS (other than exaggerated pharmacology) adverse effects in the safety pharmacology studies. RP5063 does not alter QT interval. Phase I randomized placebo and single/multiple dose in 55 subjects results showed excellent safety and tolerability with expected adverse effect profile.

**Methods:** A randomized placebo controlled Phase 1 study PK and PD of multiple, ascending oral doses of RP5063 in 32 in-patients with stable schizophrenia: 10, 20, 50 and 100 mg/day for 10 days.

**Results:** AEs included constipation, dizziness, emesis, insomnia and EPS including akathesia. No safety signals were identified in the clinical laboratory including prolactin and metabolic syndrome indices, vital signs, or ECG. PK was predictable, T ½ = 59 - 72 h. ANCOVA with baseline as covariate was used to compare groups, based on the five Marder PANSS factors. There was an overall effect for treatment vs. Placebo for the Positive Factor Score ($p = 0.007$). Moreover, repeated measures analysis revealed a reduction in the Treatment group across time ($p = 0.038$) and after controlling for baseline scores $p = 0.027$. For baseline PANSS >50, repeated measures analysis revealed a significant difference in the Treatment group across time ($p = 0.005$) and after controlling for baseline scores ($p = 0.004$). There were trends in worsening anxiety/depression and impulsivity/hostility in the placebo group. Cognitive improvement signals at certain timepoints were seen in Trails A and DSST.

**Conclusions:** RP5063's unique pharmacological profile, combined with a favourable safety profile and efficacy signal in a small short study may offer significant advantage over existing treatments for schizophrenia.

**Learning Objectives:**
- To consider translational component of receptor activity
- To evaluate early clinical data on novel antipsychotic

**Source Of Funding:** Reviva Pharmaceuticals

**Literature References:**
- Marder S et al. The effects of risperidone on the five dimension of schizophrenia derived from factor analysis: combined analysis from 5 N American trials J Clin Psych Dec 1997; 58:538-546.
- Kay S et al. Pyramidical model of schizophrenia. Schizophrenia Bulletin 1990: 16: 537-545.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## COGNITIVE EFFECTS OF MECAMYLAMINE AND VARENICLINE ON SCHIZOPHRENIA

Sungwon Roh, MD, PhD, Luke Stoeckel, PhD, A. Eden Evins, MD

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The high prevalence of smoking among people with schizophrenia compared with the general population suggests that there is an underlying biological mechanism that renders these patients more susceptible to nicotine dependence. When people quit smoking, a major symptom of nicotine withdrawal is cognitive impairment, which can make individuals more likely to resume smoking in order to ameliorate that withdrawal effect. Smokers with schizophrenia have higher smoking relapse rates than smokers in the general population, perhaps because schizophrenia patients have reduced nicotinic receptor responsiveness that is not expected to return to normal after smoking cessation. There is increasing evidence that dysregulation of the neuronal nicotinic acetylcholine receptor (nAChR) system contributes to the pathophysiology of schizophrenia. This study aimed to investigate the effects of a noncompetitive nAChR antagonist, mecamylamine, and an $\alpha 4\beta 2$ nAChR partial agonist, varenicline, on attention, working memory, and response inhibition performance. We conducted a randomized, double-blind, placebo-controlled, crossover study of a single dose of each drug on cognition in patients with schizophrenia (n=32) and healthy controls (n=57). All participants were nonsmokers in order to eliminate confounding effects of nicotine withdrawal and reinstatement that may occur in the study of smokers. Participants were administered either 10 mg of mecamylamine, 1 mg of varenicline or placebo orally. The cognitive battery was administered 3 hours after medication administration. Participants attended the 3 study days separated by 1-2 weeks. The primary outcome measure was performance on the Three Card Stroop task. A single dose of varenicline improved the performance on the interference condition of the Stroop compared to both mecamylamine and placebo in individuals with schizophrenia. In addition, this improvement did not appear in controls. Beneficial effects of varenicline on response inhibition were not accompanied by improvements in attention, vigilance, or working memory as no difference between drugs was observed on the Continuous Performance Test Identical Pairs Version, N-Back task, or Visual Spatial Working Memory task. In summary, varenicline, a nicotine partial agonist, improved response inhibition in subjects with schizophrenia. These results are supportive of the previous findings that individuals with schizophrenia derived greater cognitive benefit, specifically response inhibition, from nicotine than healthy controls. Our findings suggest that nicotine may have a clear role in cognition in nonsmokers with schizophrenia and a nicotinic partial agonist, varenicline, can be more effective on smoking cessation in schizophrenia than in general population.

**Learning Objectives:**

- To understand the effects of nicotine receptor agonist/antagonist on cognitive function
- To compare the cognitive effects of mecamylamine and varenicline on schizophrenia with those on healthy controls

**Source Of Funding:** NARSAD Young Investigator Grant

**Literature References:**

- Barr RS, et al. The effect of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacology 2008; 33: 480-90.
- Barr RS, et al. A single dose of nicotine enhances reward responsiveness in nonsmokers: Implications for development of dependence. Biological Psychiatry 2008; 63: 1061-5.

## COMPARISON OF OUTCOMES IN PATIENTS WITH EARLY PHASE VERSUS LATER PHASE SCHIZOPHRENIA

Holland C. Detke, PhD[1], Christoph U. Correll, MD[2], Chunxu Liu, PhD[3], John Landry, MS[4], Peter D. Feldman, PhD[1], David P. McDonnell, MD[1]

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**Background:** The present analyses were conducted to compare treatment outcomes for patients initiating olanzapine long-acting injection (LAI) within 5 years of onset of illness ("Early Phase" group) versus those initiating olanzapine LAI greater than 5 years after illness onset ("Later Phase" group).

**Methods:** Data were obtained from the 8 studies in the clinical trial database involving olanzapine LAI (dose range: >45 mg/4 weeks to 300 mg/2 weeks). Outcome measures included rates of and time to study discontinuation, relapse, remission, and sustained remission, as well as mean changes from baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) total and subscale scores.

**Results:** Of the 1879 patients in the analysis, 24.2% were in the Early Phase group and 75.8% were in the Later Phase group. The Early Phase group showed a longer median time to discontinuation (P=.003), longer time to relapse (P=.018), and, among patients not in remission at study initiation (45.8%), a shorter median time to sustained remission (P=.012). Rates of remission and sustained remission were also higher for the Early Phase group relative to the Later Phase group (P<.001, both measures). The Early Phase group also showed greater symptom reduction in their mean PANSS total, negative, positive, and general psychopathology scores, and in their BPRS total, positive and anxiety/depression scores (P<.01, all measures).

**Conclusions:** These findings support the assertion that clinical outcomes with use of a depot antipsychotic such as olanzapine LAI are significantly improved in patients who begin the depot earlier in the course of their illness compared with patients who begin the depot later.

**Learning Objectives:**

- Describe the difference in treatment outcomes between patients with schizophrenia either within or beyond 5 years from the onset of their illness
- Justify the use of depot antipsychotic medication in early intervention in the treatment of schizophrenia

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

**Literature References:**

- Marshall M; Rathbone J: Early intervention for psychosis. Cochrane Database Syst Rev 2011;15(6):CD004718.
- Nordentoft M; Jeppesen P; Petersen L; Bertelsen M; Thorup A: The rationale for early intervention in schizophrenia and related disorders. Early Interv Psychiatry 2009;3(suppl 1):S3-S7.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## INCIDENCE AND TIME COURSE OF EXTRAPYRAMIDAL SYMPTOMS (EPS): ORAL VS LONG-ACTING INJECTABLE (LAI) PALIPERIDONE

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**Objective:** To compare incidence and time course of EPS-related adverse events (AEs) between oral and LAI paliperidone.

**Methods:** Analysis included pooled data (safety analysis set; n=2256 for non-placebo treated patients) from randomized, double-blind and controlled paliperidone studies (3 oral [6-wks each]; 4 LAI [13-wks each]), and assessed comparable doses (oral: 3-15 mg; LAI: 25-150 mg eq [US doses 39-234 mg]). We summarized incidence rates and time of onset for EPS-related AEs, categorized by MedDRA EPS group terms. Mean values over time for AIMS (Abnormal Involuntary Movement Scale; dyskinesia), BARS (Barnes Akathisia Rating Scale; akathisia) and SAS (Simpson Angus Rating Scale; parkinsonism) were graphed.

**Results:** Mean reductions (SD) from baseline to endpoint in EPS scores were larger for LAI (AIMS: -0.10[1.27]; BARS: -0.09[1.06]; SAS: -0.04[0.20]) vs oral studies (AIMS: -0.08[1.32]; BARS: -0.03[1.24]; SAS: -0.0[0.23]). These differences favored LAI for BARS (P=0.023) and SAS (P< 0.0001) but not AIMS (P=0.49). Anticholinergic use (to treat EPS) was lower in LAI (12%) vs oral studies (17%). Incidence for all categories of spontaneously reported EPS-related AEs was highest in the first 8 treatment days though generally lower for LAI than oral. Mean values for EPS scale scores were comparable (LAI and oral) without evidence of a dose response; scores increased between days 8-15 in LAI, but not oral studies. Conclusion: Incidence of spontaneously reported EPS-related AEs was similar following exposure to LAI (~ 90 days) and oral (~ 40 days) paliperidone, at comparable doses.

**Learning Objectives:**
- To understand the incidence and time course of EPS-related events with the LAI formulation of paliperidone
- To compare this EPS incidence with that of oral formulation

**Source Of Funding:** Janssen Research & Development, LLC.

**Literature References:**
- Gopal S, et al. Number needed to treat and number needed to harm with paliperidone palmitate relative to long-acting haloperidol, bromperidol, and fluphenazine decanoate for treatment of patients with schizophrenia. Neuropsychiatr Dis Treat 2011;7: 93-101.
- Weiden P. EPS profiles: the atypical antipsychotics are not all the same. J Psychiatr Pract 2007;13: 13-24.

## WITHIN-DRUG BENEFIT/RISK OF OLANZAPINE LAI AT 1 AND 2 YEARS OF TREATMENT

Holland C. Detke, PhD[1], John Lauriello, MD[2], John Landry, MS[3], Susan B. Watson, PhD[1], David P. McDonnell[1]

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**Purpose:** To evaluate 1- and 2-year within-drug benefit/risk (B/R) of olanzapine long-acting injection (OLZ LAI).

**Methods:** Subjects were 1192 patients with the opportunity for ≥2 years OLZ LAI treatment for schizophrenia. First, frequencies of key benefits and risks were evaluated vs. average duration of those events for all patients. Next, the Transparent Uniform Risk/Benefit Overview (TURBO) method[1] was employed weighting a drug's 2 most potentially medically serious and/or frequent adverse events vs. primary benefit (effectiveness) and an ancillary benefit. Authors' independent ratings were averaged and placed on a t-score grid from 1-7 (worst balance to excellent).

**Results:** The most frequent event was remaining relapse-free (92% at 1 yr; 88% at 2 yr). Mean cumulative days without relapse was 308 at 1 yr and 549 at 2 yr. Next most frequent was meeting symptomatic remission criteria at any time (82% at 1 yr; 84% at 2 years). Incidence of weight gain ≥7% of baseline was 33% at 1 yr and 41% at 2 yr; mean days duration=53±99 at 1 yr and 121±208 at 2 yr. Per-patient post-injection delirium/sedation syndrome (PDSS) incidence was 0.7% at 1 yr and 1.5% at 2 yr; mean duration=0 days at 1 and 2 yr. For those with an event (8 patients at 1 yr; 18 at 2 yr), mean duration was 2 days at both 1 and 2 yr. For TURBO analysis, PDSS and weight gain were unanimously selected as key risks; choice of ancillary benefit varied. Mean benefit rating was 5; mean risk rating was 2.8 of a possible 7, yielding a B/R balance in the "acceptable" range (t score=5).

**Conclusion:** OLZ LAI's B/R balance was in the "acceptable" range based on TURBO ratings. Quantitative evaluation showed benefits (such as remission, relapse-free days) outweighed lower-probability events (PDSS), but higher-probability risks (weight gain) remained a significant clinical concern for many patients.

**Learning Objectives:**
- Evaluate OLZ LAI benefit/risk at 1 and 2 yrs of treatment
- Apply TURBO method

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

**Literature References:**
- Council for International Organizations of Medical Sciences (CIOMS) Working Group IV: Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Geneva, CIOMS, 1998.
- Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F: Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. Clin Pharmacol Ther 2011; 89:312-15.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## EXAMINING METHODS FOR COMPUTING "CLINICAL RESPONSE" IN PLACEBO CONTROLLED TRIALS OF ANTIPSYCHOTICS IN THE NEWMEDS REPOSITORY

Jonathan Rabinowitz, PhD[1], Nomi Werbeloff, PhD[1], François Menard, MD[2], Judith Jaeger, PhD[3], Bruce Kinon, MD[4], Virginia Stauffer, PharmD[4], Francine S Mandel, PhD[5], Shitij Kapur, MD[6]

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**Background:** Draft EMA guidelines for drug development in schizophrenia have recommended presenting responder analysis of 30% change from baseline on PANSS (1). We examined extent of clinical response using 20% and 30% thresholds in 29 placebo controlled trials of second generation antipsychotics.

**Methods:** Data are from the NEWMEDS repository of patient anonymized data from AstraZeneca, Janssen, Eli Lilly, Lundbeck, and Pfizer from 29 placebo-controlled trials of second-generation antipsychotics in schizophrenia. All studies were truncated at 6 weeks, and one study, where this was not possible, was excluded from the analysis. We examined study results using clinical response criteria of 20% and 30% change from baseline to endpoint. We computed adjusted (i.e., accounts for the fact that PANNS lowest score is 30) and unadjusted change, which are reported interchangeably in the literature (2).

**Results:** Comparing placebo (n=2024) to active treatment (n=6510), adjusted response rate was higher than unadjusted response rate for both groups at the 20% and 30% levels. Within studies, in 48% (39 of 81) of active arm comparisons to placebo, active arm had significantly higher proportion of responders at all but the 30% unadjusted level. At the 30% unadjusted level it was reduced to 30% (24 of 81). When examining studies, in 39% (11 of 28) no active treatment arms were significantly better than placebo on response at 20% adjusted and unadjusted and 30% adjusted. At the 30% unadjusted response level, 46% (13 of 28) of studies had no active treatment arms that were significantly better than placebo.

**Discussion:** In all studies, the PANSS as a continuous measure found active treatment to be significantly superior to placebo on at least some of the active treatment arms. Though not powered for responder analysis, number of responders was analyzed as secondary parameter. EMA guidelines were not specific as to how change should be computed. Substantially less analyses using unadjusted 30% change (30%) showed a significant differentiation between active vs. placebo as compared to adjusted 30% and adjusted and unadjusted 20% change (all three 46%-48%). Studies should be explicit as to how they computed change.

**Learning Objectives:**

- Understand difference in ways of computing change on the PANSS.
- Understand ramifications of different definitions of clinical response.

**Source Of Funding:** Innovative Medicines Initiative Joint Undertaking (IMI JU) n° 115008

**Literature References:**

- EMA: Guideline on clinical investigation of medicinal products in the treatment of schizophrenia, London, European Medicines Agency, 2011.
- Leucht S, et al: What does the PANSS mean? Schizophr Res 2005; 79:231-238.

## A CHEMICAL BIOLOGY APPROACH TO IDENTIFY DISEASE SIGNATURES IN SCHIZOPHRENIA AND BIPOLAR DISORDER USING IPSC-DERIVED NEURONAL CELLS: IMPLICATIONS FOR HIGH-THROUGHPUT SCREENING

Rakesh Karmacharya, MD, PhD[1,2], Steven D. Sheridan, PhD[1], Sabine Bavamian, PhD[1], Jennifer Wang, PhD[1], Kraig Theriault, BS[1], Elizabeth G.J. O'Brien, BS[1], Sigrun Gustafdottir, PhD[3], Katherine L. Madden, BS[3], Donna McPhie, PhD[2], Roy H. Perlis, MD[1], Dost Ongur, MD, PhD[2], Alykhan Shamji, PhD[3], Anne E. Carpenter, PhD[3], Bruce M. Cohen, MD, PhD[2], Stuart L. Schreiber, PhD[3,4], Stephen J. Haggarty, PhD[1]

[1]Massachusetts General Hospital, Boston, MA, [2]McLean Hospital, Belmont, MA, [3]Broad Institute of Harvard and MIT, Cambridge, MA, [4]Harvard University/HHMI, Cambridge, MA

The development of improved therapeutics for major neuropsychiatric illnesses such as schizophrenia and bipolar disorder has been hindered by the inability to undertake cellular and molecular investigations of live neuronal tissue from patients. Recent advances in the generation of induced pluripotent stem cells (iPSCs) from human fibroblasts provide for a new way to generate neuronal cultures with the patients' genetic makeup.

We are reprogramming human fibroblasts using defined genetic factors to to generate iPSCs from patients with schizophrenia and bipolar disorder as well as from matched controls. We differentiate iPSCs into neural progenitor cells (NPCs) which are further differentiated along the neuronal lineage. We will acquire high-content images of NPC-derived neuronal cells and label them with neuronal subtype-specific markers as well as a range of cellular stains. We will analyze the high-content images to quantify a range of cellular and sub-cellular features (e.g. numbers, lengths, branching patterns of dendrites, quantity/localization of mitochondria etc.). In addition to normal conditions, we intend to collect images of neuronal cultures treated with an annotated set of 300 small molecules comprised of known inhibitors/activators of various signaling pathways as well as small molecules/drugs that are known to modulate neuronal and glial biology. While disease-related phenotypic features may not be readily visible at baseline, perturbation of specific signaling pathways may expose cellular deficits inherent to the biology of the disease neurons. We will use machine-learning algorithms to identify features that distinguish neurons derived from schizophrenia and bipolar disorder iPSCs from neurons derived from healthy controls. If a specific small molecule elicits different phenotypic responses in disease neuronal cells vis-à-vis control cells, we will carry out RNAi knockdown of the target to recapitulate the different effects observed with small molecules. The identification of differential responses to small molecule/RNAi will also give important clues on the underlying pathways that may be aberrant in the diseased neuronal cells. Using this methodology, we will carry out unbiased phenotypic profiling of the neuronal cells and extract "disease signatures" that can be used for high-throughput screens.

Understanding the cellular pathophysiology underlying schizophrenia and bipolar disorder can lead to the identification of new therapeutic targets and the development of improved therapeutics for schizophrenia and bipolar disorder. Recent advances in stem cell research and chemical biology provide new avenues to investigate disease biology and develop new therapeutic leads for schizophrenia and bipolar disorder. We present an approach to generate and characterize patient iPSC-derived neuronal cells in the presence of a range of small molecule perturbations in order to identify disease-specific cellular signatures. We discuss our approach to use these "disease signatures" to screen for small molecules that modulate or "normalize" the disease-related cellular signatures in order to develop new leads for therapeutic development.

**Learning Objectives:**

- Harnessing novel techniques in chemical biology and stem cell biology to address issues of importance to psychiatric disease biology
- Approaches to using high-throughput screening to identify probes for studying disease biology and to identify novel small molecules as leads for therapeutic development

**Source Of Funding:** National Institute of Health 5K08MH086846, Harvard Stem Cell Institute, NARSAD

**Literature References:**

- Takahashi K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007 131:861-72.
- Marchetto M, et al. A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. Cell 2010 143:527-39.
- Schreiber SL. Organic synthesis toward small-molecule probes and drugs. Proc Natl Acad Sci U S A. 2011 108:6699-702.
- Sheridan S, et al. Epigenetic characterization of the FMR1 gene and aberrant neurodevelopment in human induced pluripotent stem cell models of fragile X syndrome. PLoS One. 2011 6:e26203.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## PNB02: A BENEFICIAL TREATMENT FOR INSUFFICIENT RESPONSE WITH SINGLE AGENT TREATMENT IN SCHIZOPHRENIA?

Erik Buntinx, MD[1], Ludo Haazen, MD[1], Didier de Chaffoy, PhD[1], Philip D. Harvey, PhD[2]

[1]PharmaNeuroBoost NV, Alken, Belgium, [2]University of Miami, Miami, Florida

Efficacy of schizophrenia treatment is often hampered as severe adverse events (AE) can occur when doses of antipsychotic drugs are titrated upwards. To reach the necessary efficacy, psychiatrists often combine various typical and atypical antipsychotics, though safety and efficacy of this approach is not evidence-based (Nasrallah, 2010; Barnes & Patton, 2011). Use of clozapine (CLO), although more effective is limited due to the risk for severe AE and high follow-up costs.

Therefore, an antipsychotic agent with an efficacy comparable to CLO and a potentially better AE profile compared to atypical antipsychotics would satisfy a major unmet medical need and represent a break-through. Such agent should ideally have a receptor binding profile similar to that responsible for the superior efficacy of CLO (central 5-HT2A blockade and D4 blockade over D2 blockade(Goodman & Gilman, 11th ed.)), without binding to those receptors responsible for its AE.

This pharmacological concept could be realized by combining the receptor binding profiles of risperidone (RIS)/paliperidone (PAL) (central 5-HT2A and D2 blockade) and pipamperone (PIP) (highly selective, combined 5-HT2A and D4 antagonist (Leysen et al., 1998)).

PNB02 is a novel pharmacological agent which, by combining low doses of PIP (15 mg/d) with the lowest effective dose of RIS or PAL is expected to significantly block central 5-HT2A and D4 receptors in combination with a moderate D2 blocking, thereby mimicking the pharmacology of CLO without affecting those receptors responsible for its AE.

Study results so far confirm PNB02's potential selective nature, absence of drug interactions between constituent agents and a comparable receptor binding profile to CLO (Data on file).

A phase I/IIa multicenter DB RCT in 60 chronic schizophrenic or schizoaffective patients stabilized with long acting (LA) RIS/PAL but with residual psychotic symptoms is ongoing. Objectives are to explore the effect on fMRI of adding single dose PIP, and to assess clinical outcome over 6 weeks of treatment with PIP + LA RIS/PAL vs. LA RIS/PAL alone.

Above data suggest PNB02 could have an efficacy comparable to CLO. PNB02's constituent elements have been extensively studied and are expected to cause only moderate side-effects. PNB02 is therefore of potential value for schizophrenia patients insufficiently responding to single agent treatment and could represent a safe and effective alternative to poly-pharmacy.

Pre-clinical, phase I and PK/PD modeling data will be presented, as well as the rationale and design of the phase I/IIa Proof of Concept program aiming to demonstrate beneficial effects in schizophrenic patients suffering from residual symptoms.

**Learning Objectives:**

- Gain insight into current treatment of schizophrenia and its shortcomings
- Understand how PNB, through innovate drug design based on complementary receptor binding profiles of different agents develops novel therapeutic concepts
- Understand why PNB02 could be a beneficial treatment in case of insufficient response with single agent treatment
- Understand study results and research strategy for PNB02

## LURASIDONE FOR THE ACUTE TREATMENT OF ADULTS WITH SCHIZOPHRENIA: WHAT IS THE NUMBER NEEDED TO TREAT, NUMBER NEEDED TO HARM, AND LIKELIHOOD TO BE HELPED OR HARMED?

Leslie Citrome, MD

Leslie Citrome, MD, MPH, Suffern, NY

**Objective:** To describe the efficacy, safety and tolerability of lurasidone for the acute treatment of schizophrenia using the metrics number needed to treat (NNT) and number needed to harm (NNH).

**Methods:** Study data were pooled from the six phase II and III, 6-week, randomized placebo-controlled trials that were conducted to test the efficacy and safety of lurasidone for the acute treatment of schizophrenia. Included were the following interventions: fixed doses of lurasidone 20, 40, 80, 120 and 160 mg/d; haloperidol 10 mg/d; olanzapine 15 mg/d; quetiapine extended-release 600 mg/d; placebo. The following outcomes were assessed: responder rates as defined by a reduction of ≥20, 30, 40 or 50% from baseline on the Positive and Negative Syndrome Scale (PANSS); study completion; discontinuation due to an adverse event (AE); weight gain ≥7% from baseline; incidence of spontaneously reported AEs; incidence of total cholesterol ≥240 mg/dl, low-density lipoprotein cholesterol ≥160 mg/dl, fasting triglycerides ≥200 mg/dl and glucose ≥126 mg/dl at endpoint. NNT for the efficacy outcomes and NNH for the safety/tolerability outcomes were calculated. Likelihood of being helped or harmed (LHH) was also calculated to illustrate trade-offs between outcomes of improvement ≥30% on the PANSS vs. incidence of akathisia, nausea, sedation, somnolence and parkinsonism.

**Results:** NNT vs. placebo for PANSS reductions ≥30% were 8, 7, 7 and 4 for lurasidone doses of 40, 80, 120 and 160 mg/d, respectively, and 4 and 3 for olanzapine 15 mg/d and quetiapine extended-release 600 mg/d, respectively. Lurasidone was not associated with any statistically significant disadvantages over placebo for weight gain or metabolic abnormalities; NNH vs. placebo for weight gain ≥7% from baseline was 4 for olanzapine and 9 for quetiapine extended-release in contrast to a NNH for this outcome ranging from 43 to 150 for lurasidone 40-160 mg/d. The 5 most consistently encountered adverse events attributable to lurasidone were akathisia, nausea, sedation, somnolence and parkinsonism, with NNH vs. placebo for lurasidone 40-120 mg/d ranging from 6 (akathisia with 120 mg/d) to 30 (parkinsonism with 80 mg/d). Lurasidone 160 mg/d appeared better tolerated than doses of 40, 80 or 120 mg/d for akathisia, nausea, sedation or somnolence, with no NNH values for these adverse events for 160 mg/d vs. placebo being statistically significant. LHH was favorable for lurasidone when contrasting PANSS reductions vs. adverse events.

**Conclusions:** NNT and NNH can help quantify efficacy, safety and tolerability outcomes and place lurasidone into clinical perspective. Advantages for lurasidone include a low propensity for weight gain and metabolic abnormalities. More commonly encountered adverse events include akathisia, nausea, sedation, somnolence and parkinsonism, but NNH values are generally in the double digits, reflecting an overall tolerable profile. Individual patient characteristics, values and preferences will need to be considered when selecting lurasidone over other antipsychotics.

**Learning Objectives:**

- To understand the efficacy profile of lurasidone using the metric of number needed to treat (NNT)
- To understand the tolerability of lurasidone using the metric of number needed to harm (NNH)
- To understand tradeoffs between NNT and NHH using the ratio of likelihood to be helped or harmed (LHH)

**Literature References:**

- Citrome L. Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. Int J Clin Pract 2011;65(2):189-210.
- Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. Acta Psychiatr Scand 2008;117(6):412-9.
- Citrome L. Number needed to treat: What it is and what it isn't, and why every clinician should know how to calculate it. J Clin Psychiatry 2011;72(3):412-3.
- Citrome L. Quantifying risk: the role of absolute and relative measures in interpreting risk of adverse reactions from product labels of antipsychotic medications. Curr Drug Saf 2009;4(3):229-37.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## BLEAK HOUSE: A STUDY OF SCHIZOPHRENIA IN THE ERA OF DEINSTITUTIONALIZATION

Reuven Ferziger, MD[1], Lian Mao, PhD[2], Cynthia A. Bossie, PhD[1], Larry Alphs, MD, PhD[1]

[1]Janssen Scientific Affairs, LLC, Titusville, NJ, [2]Johnson & Johnson Pharmaceutical Research & Development, LLC, Titusville, NJ

**Introduction:** Overrepresentation of people with serious mental illness (SMI) in the criminal justice system (CJS) is an important public health problem. Yet this is a poorly studied patient population, as few clinical trials specifically study SMI offenders and most operate within idealized conditions limiting eligibility. This analysis examines population characteristics in an ongoing comparative effectiveness trial of antipsychotic treatment for people with schizophrenia released from incarceration and pooled data from pivotal trials of the same drug conducted for regulatory approval.

**Methods:** Sample 1 (NCT01157351) is from an ongoing 15-month randomized, open-label, multicenter US study comparing paliperidone palmitate with oral antipsychotics in a community sample of subjects with schizophrenia released from incarceration. Sample 2 is pooled data from completed short-term, randomized double-blind international studies of paliperidone palmitate in subjects with schizophrenia. Descriptive statistics evaluated baseline demographics and clinical characteristics of enrolled subjects. Two sample t-tests and chi-square tests used to compare groups. No adjustments made for multiplicity.

**Results:** Statistically significant differences (P<=0.01) between samples 1 (N=280) and 2 (N=1803) included mean (SD) age (37.2 [10.3] vs 39.8 [10.8] y), sex (percentage males, 87.9% vs 67.6%); race (percentage African Americans, 62.9% vs 30.5%); mean (SD) age of first psychiatric diagnosis (19.7 [7.3] vs 25.7 [8.5] y); and severity of illness (percentage borderline or mildly ill at study entry via CGI-S score, 33.7% vs 3.6%).

**Conclusion:** Baseline data from these 2 schizophrenia samples differed in several categories. The relationship to outcomes parameters will be explored.

**Learning Objectives:**

- Compare baseline demographics and clinical characteristics of patients with schizophrenia who were in the criminal justice system vs those who were not in the system
- Educate participants on the incidence of psychiatric disorders within the criminal justice system

**Literature References:**

- Baillargeon J, Binswanger IA, Penn JV, Williams BA, Murray OJ. Psychiatric disorders and repeat incarcerations: the revolving prison door. Am J Psychiatry. 2009;166(1):103-9.
- Steadman HJ, Osher FC, Robbins PC, Case B, Samuels S. Prevalence of serious mental illness among jail inmates. Psychiatr Serv. 2009; 60(6):761-5.

## COGNITIVE PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH LURASIDONE: RESULTS FROM A 6-WEEK CORE STUDY AND 6 MONTH DOUBLE-BLIND EXTENSION

Philip D. Harvey, PhD[1], Cynthia Siu, PhD[2], Josephine Cucchiaro, PhD[3], Antony Loebel, MD[3]

[1]University of Miami Miller School of Medicine, Miami, FL, [2]Data Powers, Inc, Ringoes, NJ, [3]Sunovion Pharma, Marlborough, MA

**Background:** Cognitive impairment is a core feature of schizophrenia. This multiregional study of lurasidone in schizophrenia, consisted of a 6-week, double blind, placebo- and active-controlled study, followed by a 12-month, double-blind extension. Results of a computerized cognitive battery (CogState) evaluating change in cognitive performance, from acute study baseline to 6-month extension endpoints, are reported here.

**Methods:** Clinically unstable patients with schizophrenia were randomized to once-daily treatment with lurasidone 80 mg (n=125), lurasidone 160 mg (n=121), quetiapine XR 600 mg (n=120) or placebo (n=122). Subjects who completed the 6-week trial were eligible to enroll in a double-blind extension study, involving flexible treatment with once-daily doses of lurasidone (40-160 mg; n=151, LUR) or quetiapine XR (200-800 mg; n=85, QXR). Subjects initially treated with PBO were started on LUR (n=56). Cognitive performance was examined with the CogState system at baseline, 6 weeks, and at 3 and 6 months in the extension phase.

**Results:** In the acute period, task completion rates averaged 94%, but data integrity failureswere noted in 23% of the cases. At 6 weeks, no statistically significant differences in the CogState composite score were found between lurasidone dose groups, the active control and the placebo group in the full ITT sample (N=488). When patients whose data failed the prespecified integrity checks were excluded in a secondary analysis (N=267), LUR160 was superior on the cognitive composite score to both PBO (p<0.05, d=.25) and QXR (p<0.05, d=.28), while QXR, LUR80, and PBO did not differ . UPSA-B scores were also superior to PBO at 6 weeks for all active treatments. In the extension study, we found a cognitive benefit for LUR compared to QXR treated patients, assessed from core baseline to the week-32 (6-month) endpoint.

**Conclusions:** This is the first pharmacological study to date where the investigational treatment was superior to placebo on cognitive assessments and a functional co-primary measure (at 6-week endpoint), as well as demonstrating superiority to an active comparator on neurocognitive improvement over a 6-week acute phase and a 6-month extension . These findings require replication, but cannot be attributed to practice effects due to placebo controls. Levels of data integrity failures were high compared to that of previous trials that used other cognitive assessments, such as the MCCB.

**Learning Objectives:**

- To understand the potential benefits of high-dose lurasidone treatment on cognition
- To understand whether long-term treatment with atypical medications leads to sustained benefits

**Source Of Funding:** Sunovion Pharma

**Literature References:**

- Harvey PD, et al., Performance and Interview-based Assessments of Cognitive Change in a Randomized, Double-blind Comparison of Lurasidone vs. Ziprasidone. Schizophr Res, 2011. 127, 188–194.
- Goldberg, T.E.,et al., Cognitive improvement after treatment with second-generation antipsychotic: medications in first-episode schizophrenia: is it a practice effect? Arch. Gen. Psychiatry 64 (10), 1115–1122.
- Keefe RS,. et al. (2007) . Neurocognitive Effects of Antipsychotic Medications in Patients with Chronic Schizophrenia in the CATIE Trial. Arch Gen Psychiatr; 64:633-647.
- Ishiyama T, et al., 2007. Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test. Eur J Pharmacol 572:160-170.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## A PILOT STUDY OF COGNITIVE REMEDIATION IN A FORENSIC SETTING

Anthony O. Ahmed, PhD

Georgia Health Sciences University, Augusta, GA

**Introduction:** Cognitive remediation is a behavioral strategy shown to improve neurocognition, information processing, and quality of life for people with schizophrenia. It has garnered enthusiasm for its potential to address the limitations of psychopharmacological treatment at attenuating cognitive deficits. Systematic evaluations of cognitive remediation in schizophrenia are however in relative infancy. Most studies have focused on recently hospitalized patients or outpatient samples with only moderate levels of impairment. No studies have evaluated the benefit of this intervention for people receiving services in forensic settings. We designed a project to evaluate the benefits of cognitive remediation for patients at a state hospital with more severe cognitive deficits and disability than currently represented in the literature. We drew participants from a short-term admission unit and a long-term forensic unit, most of whom had been adjudged as ~~In~~competent to Stand Trial" or ~~N~~ot Guilty by Reason of Insanity".

**Aims:** We are seeking to address the following questions:
Does computerized cognitive remediation result in improvements in cognitive skills and functional capacity? What variables are predictive of improvements following cognitive remediation – age, age of onset of psychopathology, onset type (chronic versus acute), course (simple versus episodic), predominant symptoms, and premorbid intellectual functioning?

**Hypothesis:** Participation in cognitive remediation will result in improvements in cognitive processes including attention, verbal and visual memory, processing speed, reasoning, and cognitive flexibility. Participation will lead to improvements in measures of recovery attitudes and functional capacity.

**Method:** A randomized control trial will allow us to compare the outcomes of individuals who participate in cognitive remediation with individuals in a Treatment As Usual condition following the intervention and at follow-up. Cognitive remediation is being provided by masters-level clinicians at the hospital.

**Participants:** Patients with schizophrenia recruited from the hospital units.

**Measures:** We administered the following measures at baseline:
Defeatist Beliefs Subscale – Dysfunctional Attitudes Scale (DAS)
Demographics and Clinical Characteristics Questionnaire.
Maryland Assessment of Recovery Scale (MARS)
MATRICS Consensus Cognitive Battery (MCCB)
Positive and Negative Syndrome Scale (PANSS)
The UCSD Performance-Based Skills Assessment (UPSA)
Wechsler Abbreviated Scale of Intelligence (WASI)
We will administer the primary outcome measures — the MARS, UPSA, and the MCCB post-intervention, and at a three-month follow-up following completion of the intervention.

**Status:** Baseline data has been collected on an initial sample of 36 individuals who were randomly assigned to one of the study conditions. The treatment phase has commenced and posttreatment data would be completed in April 2012.

**Learning Objectives:**

- Understand the rationale for implementing cognitive remediation for schizophrenia patients in a forensic setting.
- Learn the results of the pilot trial on cognitive remediation.

**Source Of Funding:** None

**Literature References:**

- McGurk SR, Twamley EW, Sitzer DI, et al. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry. 2007;164:1791-1802.
- Fisher M, Holland C, Merzenich MM, Vinogradov S. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. Am J Psychiatry. 2009;166:805-811.
- Lindenmayer JP, McGurk SR, Mueser KT, et al. A randomized controlled trial of cognitive remediation among inpatients with persistent mental illness. Psychiatr Serv. 2008;59:241-247.

## THE IMPACT OF STUDY DESIGN IN COMPARATIVE EFFECTIVENESS RESEARCH IN SCHIZOPHRENIA

Noam Y. Kirson, PhD[1], Bruce J. Wong, MD[2], Yermakov Sander, MS[1], Wayne Huang[1], Thomas Samuelson[1], Steve Offord, PhD[3], Greenberg E. Paul, MS[1]

[1]Analysis Group, Inc., Boston, MA, [2]Bruce Wong Consulting, Wayne, PA, [3]Otsuka America Pharmaceutical, Inc., Princeton, NJ

**Background:** Randomized controlled trials (RCTs) and observational studies (prospective and retrospective) have yielded inconsistent results when comparing oral and depot formulations of antipsychotics, highlighting the question of how research design affects estimates of comparative effectiveness (CE). We build on a cross-design synthesis methodology[1] to quantify the effect of study design on the CE of antipsychotic formulations.

**Methods:** A search of English literature since 2000 for studies with depot and oral antipsychotic treatment arms for schizophrenia with relapse, hospitalization or all-cause discontinuation as key endpoints. Average baseline characteristics were used to adjust endpoints for age and gender. Adjusted endpoints were converted to risk ratios (RR) [depot/oral; RR<1 favors depot] and pooled by study design (RCT, prospective, and retrospective). Meta-analysis with random effects[2] was used to estimate the pooled RR and 95% confidence interval (CI) of all endpoints combined within each study design. The ratios of resulting point estimates were used to calculate average conversion factors between study designs.

**Results:** 13 studies (5 RCTs and 8 observational studies) with 19 depot-oral comparisons were included. Meta-analysis of adjusted endpoints resulted in RR [CI] of 0.88 [0.64-1.20] for RCTs, 0.62 [0.48-0.81] for prospective and 0.56 [0.44-0.71] for retrospective studies. These imply conversion factors of 1.41 and 1.57 between RCTs and prospective and retrospective designs, respectively.

**Conclusions:** Depot antipsychotics display increasing effectiveness compared with oral formulations as study design shifts from RCTs towards real-world clinical settings. Differences in control over compliance exerted in the respective designs could be a contributing factor. The estimated conversion factors quantify the average effect of study design on CE and facilitate comparison across studies.

**Learning Objectives:**

- Understand effect of study design on comparative effectiveness in schizophrenia
- Understand application of cross-design synthesis methodology

**Source Of Funding:** Otsuka America Pharmaceutical, Inc.

**Literature References:**

- Droitcour J, et al. A new form of meta-analysis for combining results from randomized clinical trials and medical-practice databases. Int J Technol Assess Health Care. 1993; 9(3):440-9.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177-88.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## SWITCHING TO LURASIDONE IN SCHIZOPHRENIA: TOLERABILITY AND EFFECTIVENESS OF THREE STRATEGIES

Joseph P. McEvoy, MD[1], Leslie Citrome, MD[2], David Hernandez[3], Joseph Severs, MS[3], Josephine Cucchiaro, PhD[3], Antony Loebel, MD[3]

[1]JUH Clinical Research and Duke University Medical Center, Butner, NC, [2]New York Medical College, Pomona, NY, [3]Sunovion Pharmaceuticals Inc., Fort Lee, NJ

**Objective:** To evaluate the effectiveness of switching clinically stable, residually symptomatic patients with schizophrenia or schizoaffective disorder to lurasidone.

**Method:** Not acutely ill patients with schizophrenia or schizoaffective disorder were randomized to 1 of 3 switch strategies: group 1 (n=74) started on lurasidone 40 mg/d for 2 weeks; group 2 (n=88) started on a 40 mg/d for 7 days, then increased to 80 mg/d after day 7; and group 3 (n=82), started at 80 mg/d for 14 days. All patients were then treated for an additional 4 weeks with flexibly-dosed lurasidone 40-120 mg/d. Time to treatment failure was evaluated, defined as insufficient clinical response, exacerbation of underlying disease or discontinuation due to an adverse event (AE). Patients were also stratified based on whether the pre-switch antipsychotic was sedating (olanzapine, quetiapine) or non-sedating (all others).

**Results:** No clinically relevant differences in efficacy or tolerability were noted when comparing the 3 different switch strategies. The cumulative treatment failure for all switch strategies combined was 7.9%. Treatment failure was reported for 10 of 86 patients (11.6%) who had previously received a sedating antipsychotic and for 9 of 154 patients (5.8%) previously treated with a non-sedating antipsychotic. Treatment with lurasidone was associated with LS mean within-group improvement at endpoint on the PANSS of -5.8 (95%-CI, -7.0, -4.5; Cohen's d, 0.5). For the total sample, treatment with lurasidone was associated with -0.3 kg mean decrease in weight, and a reduction in median levels of both total cholesterol and triglycerides.

**Conclusions:** In this study, switching to lurasidone was safe and well-tolerated using a cross-taper strategy regardless of initial lurasidone dose or titration scheme. Patients switched to lurasidone demonstrated clinically relevant improvement in efficacy measures, and reduction in weight and lipids.

**Learning Objectives:**

- Understand the role of switching strategies for the management of schizophrenia
- Learn about the safety and efficacy outcomes of switching from another atypical antipsychotic to lurasidone

**Source Of Funding:** Funded by Sunovion Pharmaceuticals Inc.

**Literature References:**

- Meltzer HY et al. Lurasidone in the treatment of schizophrenia. Am J Psychiatry 2011;168:957-67.
- Citrome L. Lurasidone for schizophrenia: a brief review. Clin Schizophr Relat Psychoses 2011;4:251-7.

## EVALUATION OF THE ACCURACY OF APPLYING ITEM RESPONSE THEORY (IRT) LINKING TO AN ABBREVIATED VERSION OF THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) FOR EVALUATION AND REFINEMENT

Anzalee Khan, PhD[1], Jean-Pierre Lindenmayer, MD[2], Charles Lewis, PhD[3], Saurabh Kaushik, MD[4]

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**Background:** Item Response Theory (IRT) is being increasingly applied to psychiatric measures for evaluating and refining of existing psychometric instruments. IRT deﬁnes a scale for the underlying latent variable (PANSS level of psychopathology) that is being measured, and items are linked with respect to this same scale. This study is an extension of our study utilizing an IRT method to create an abbreviated version of the PANSS (19-item 'Mini-PANSS') and tests the IRT linking of scores on the Mini-PANSS that correspond to a given summed score of the 30-item PANSS presented in the derived summed-score-to-IRT-score translation tables (Khan et al., 2012).

**Method:** The dataset included a validation subsample of 3594 patients with schizophrenia participating in antipsychotic trials with baseline data on the PANSS. Two sample sizes were randomly extracted: N= 1000 was chosen to represent the practice of linking items with relatively large samples in order to produce linking results. N = 500 was chosen to represent the minimum sample size in practice that is likely to yield acceptable linking results. For the 3 Mini-PANSS subscales (Positive, Negative and General Psychopathology), the corresponding 30-item PANSS subscales was evaluated. Factors manipulated in the analysis were sample size (500 or 1000), and the level of psychopathology. Mean square errors were estimated, where small mean squared error means that the randomness reflects the data more accurately than a larger mean squared error. The accuracy or performance of the IRT linking procedures was evaluated, first, in terms of recovery of the underlying level of psychopathology (true mean and SD). The ability of the procedure to recover the item parameters was evaluated using the item characteristic curve (ICC) criterion and the test characteristic curve (TCC) criterion.

**Results:** The mean square error (MSE = 0.08) showed excellent performance in item subscale linking across various levels of psychopathology (PANSS total score from 32 to 114). For N=500, the average means across the linking procedure range -.01 and .03. For N=1,000, the average means and SDs range -.01 and .02. As the sample size increased, 500 to 1,000, the accuracy of the linking method remained the same, and both ICC and TCC criterion values did not significantly change. For the Positive subscale, the mean difference between the score from the Mini-PANSS and the PANSS was -0.492 (- 4 to 2 range of scores). For the Negative Symptoms subscale, the mean difference between the score from the Mini-PANSS and the 30-item PANSS was -0.297 (- 2 to 3 range of scores). For the General Psychopathology subscale, the mean difference between the score from the Mini-PANSS and the PANSS was -0.347 (- 3 to 3 range of scores). For the PANSS total score, the mean difference between the score from the Mini-PANSS and the PANSS was -0.428 (-4 to 4 range of scores). The small mean differences and range of scores support the similarities with the original scale.

**Conclusions:** The summed-score linking method was an effective and consistent estimator that produced accurate estimates of transformation of scores on the Mini-PANSS to the PANSS when sample size and level of psychopathology were purposely manipulated. Future studies are proposed to perform filed testing of the Mini-PANSS as trials may benefit by incorporating the Mini-PANSS for less administration time and patient burden, with the ability to compare scores to the PANSS.

**Learning Objectives:**

- At the end of the poster presentation, the audience will develop an understanding of how to use statistical procedures to link scores on psychometric scales
- The audience will gain an understanding of how to refine a rating scale or psychometric instrument to adapt to clinical practice.

**Source Of Funding:** Funding was not obtained for this project. It is an extension of a dissertation project.

**Literature References:**

- Khan A et al Use of NON-PARAMETRIC Item Response Theory to develop a shortened version of the Positive and Negative Syndrome Scale (PANSS), BMC Psychiatry, 2012; 11:178.
- Orlando M, Sherbourne CD, Thissen D: Summed-score linking using item response theory: Application to depression measurement. Psychol Assessment 2000; 12:354-359.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## SAFETY AND TOLERABILITY OF CARIPRAZINE IN THE LONG-TERM TREATMENT OF SCHIZOPHRENIA: RESULTS FROM A 48-WEEK EXTENSION STUDY

Andrew J. Cutler, MD[1], Anjana Bose, PhD[2], Suresh Durgam, MD[2], Raffaele Migliore[2], Qing Wang, PhD[2], Adam Ruth, PhD[3], György Németh, MD, PhD[4], István Laszlovszky, PhD, PharmD[4]

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**Objective:** Cariprazine is an orally active, potent dopamine $D_3$-preferring $D_3/D_2$ receptor partial agonist under development for the treatment of schizophrenia. This open-label extension study evaluated the long-term safety, tolerability, and pharmacokinetics of cariprazine in patients with schizophrenia.

**Methods:** Male and female patients with schizophrenia who completed 6 weeks of double-blind treatment with placebo, cariprazine 1.5, 3.0, 4.5 mg/day, or risperidone 4.0 mg/day in the lead-in study (NCT00694707) and responded to treatment (Clinical Global Impressions-Severity [CGI-S] ≤3 and ≥20% reduction in Positive and Negative Syndrome Scale [PANSS] total score at endpoint of the lead-in study) were eligible to enroll in this extension study (NCT00839852). The extension study comprised open-label treatment with flexible-dose cariprazine 1.5-4.5 mg/day for 48 weeks. Efficacy evaluations included PANSS and CGI-S scales. Safety evaluations included adverse events (AEs), vital signs, laboratory measures, ECG, ophthalmology examinations, and assessments on the Barnes Akathisia Rating Scale (BARS) and the Simpson-Angus Scale (SAS).

**Results:** A total of 93 patients entered the open-label extension study and received cariprazine; 49.5% completed 48 weeks of open-label treatment with cariprazine. The mean duration of treatment with cariprazine was 222 days. In patients entering the extension study, PANSS and CGI-S scores decreased over the course of the study. Serious AEs (SAEs) were reported in 12.9% of patients including 1 death (suicide) during the open-label treatment period. The most common SAEs were worsening of schizophrenia (4.3%) and psychotic disorder (2.2%). Treatment-emergent AEs (TEAEs) were reported in 82.8% of patients. TEAEs reported in at least 10% of patients were akathisia (14.0%), insomnia (14.0%), and weight increased (11.8%). Mean changes in clinical laboratory values, blood pressure and pulse rate, and ECG parameters were generally small. No potentially clinically significant (PCS) changes in ECG parameters were observed and no patients had a QTc increase >60 msec. The incidence of treatment-emergent parkinsonism (SAS >3) was 8.6% and the incidence of treatment-emergent akathisia (BARS >2) was 17.2%. No patient discontinued because of movement disorder-related TEAEs.

**Conclusions:** Cariprazine 1.5-4.5 mg/day administered for up to 1 year was generally well tolerated, with relatively few new AEs associated with long-term administration and no clinically meaningful changes in the majority of safety parameters.

**Learning Objectives:**

- At the conclusion of this session, the participant should be able to evaluate the long-term tolerability of cariprazine in the treatment of schizophrenia.
- At the conclusion of this session, participants will be able to discuss the cariprazine treatment metabolic and safety profile.

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

**Literature References:**

- Kiss B: 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.
- Gyertyán I: Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. Neurochem Int. 2011;59(6):925-35.

## THE EFFECT OF THE Á2-ADRENERGIC RECEPTOR ANTAGONIST FLUPAROXAN ON A COMT-VAL-TG MOUSE MODEL OF COGNITIVE DYSFUNCTION

Ayana A. Gibbs, BS, MD, PhD

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**Objective/Hypothesis:** Cognitive dysfunction is a highly disabling feature of a number of neuropsychiatric disorders including schizophrenia, bipolar affective disorder, depression and attention deficit hyperactivity disorder (ADHD). Developing disease-modifying and symptomatic therapies for cognitive dysfunction is therefore a major goal of drug development (Searles et al. 2008). Yet it is increasingly recognised that the effects of therapeutic drugs may be dependent on individual differences due to genetic variation. The aim of this study is to examine the effect of the á2 antagonist, fluparoxan, on cognition, and the contribution of COMT genetic variation to this effect. The hypothesis under investigation is that fluparoxan treatment will significantly enhance cognitive performance in transgenic mice overexpressing the COMT val variant (COMT-Val-tg mice), but will have limited or no effect in control mice.

**Method/Proposed Methods:** The effect of fluparoxan on memory performance on the Novel Object Recognition Task (NORT) (Ennaceur and Meliani, 1992)will be evaluated in adult male COMT-Val-tg mice (Papaleo et al. 2008) and control mice (12 per group) using a within subject design. Immediately following an acquisition phase, fluparoxan (1mg/kg dissolved in 10ml/kg saline) or vehicle (same volume of saline) will be administered via intraperitoneal injections followed by a 5 minute retention test after 1 hr. Testing sessions will be videotaped and time spent exploring each object will be scored from the videotapes. This task will be repeated subsequently in the same animals that will receive the alternate intervention with care will taken to ensure prior return to baseline levels of exploration. In addition, locomotor activity will be assessed to ensure that differences in performance are not confounded by differences in activity levels. Object discrimination as a marker of memory performance will be assessed by calculating a preference index (percentage of total object exploration time spent exploring the novel object). Differences in preference index between groups will be assessed by analysis of variance with drug treatment as a within subject factor and genotype and as a between subject factors.

**Discussion/Significance:** It is anticipated that there will a significant group by genotype interaction such that the preference index will be significantly greater in COMT-Val-tg mice treated with fluparoxan compared to vehicle whereas there will be no significant effect of drug treatment on the preference index in control mice. This will provide proof of concept support for a genotype dependent cognitive enhancing effect of fluparoxan and its further evaluation as a cognitive enhancer.

**Learning Objectives:**

- To establish whether treatment with fluparoxan enhances cognitive performance in mice
- To establishc whether effects of fluparoxan on cognitive performance are genotype dependent

**Source Of Funding:** University of Sussex Enterprise Development Fund

**Literature References:**

- Ennaceur, A., et al (1992). Effects of physostigmine and scopolamine on rats' performances in object-recognition and radial-maze tests. Psychopharmacology 109, 321-330.
- Papaleo, F., et al (2008). Genetic Dissection of the Role of Catechol-O-Methyltransferase in Cognition and Stress Reactivity in Mice. The Journal of Neuroscience 28, 8709-8723.
- Searles, J. et al (2008). Cognitive Dysfunction. Decision Resources Inc: Waltham, MA.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## NEW RESULTS ALTER BALANCE OF EVIDENCE OF LONG-ACTING INJECTABLE VS. ORAL ANTIPSYCHOTICS REGARDING RELAPSE PREVENTION IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Taishiro Kishimoto, M.D., Ph.D.[1], Alfred Robenzadeh, M.D.[1], Claudia Leucht, M.D.[2], Stefan Leucht, M.D.[2], Koichiro Watanabe, M.D., Ph.D.[3], Masaru Mimura, M.D., Ph.D.[3], John M. Kane, M.D.[1], Christoph U. Correll, M.D.[1]

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**Objective:** Latest meta-analysis compared depot versus oral medication reported superiority of depot medication in relapse prevention (Leucht et al.). Since then, there are several large pragmatic trials conducted and showed no benefit of depot/long acting injection (LAI) over oral medication (Rosenheck et al.).

**Methods:** Systematic review/meta-analysis of RCTs lasting ≥6 months comparing LAIs and OAPs. Primary outcome was study-defined relapse; secondary outcomes included relapse at 3, 6, 12, 18, 24 months, drug inefficacy (i.e., relapse + discontinuation due to inefficacy), all-cause discontinuation, discontinuation due to adverse events, hospitalization, and non-adherence. Analyses were conducted in patients taking ≥1 dose (~~"sa~~safety and/or efficacy population") and the ~~"r~~randomized population". Random effects pooled relative risk (RR) with 95%CIs was calculated.

**Results:** Across 21 RCTs (n=5,130), LAIs were similar to OAPs for relapse prevention (25.9% vs. 31.4%, p=0.35, $I^2$=58%; $I^2$=38% after removing one study) and all secondary outcomes in the safety/efficacy population. This lack of superiority of LAIs was unchanged when only outpatient studies lasting ≥1 year were analyzed. Individually, only fluphenazine LAIs showed significant superiority over OAPs regarding relapse (p=0.02), drug inefficacy (p=0.002) and hospitalization (p=0.04). First-generation antipsychotics (FGA)-LAIs, but not second-generation antipsychotics-LAIs were superior to OAPs in several relapse related outcomes. However, there were also effects of publication year, in that LAIs were superior to OAPs in RCTs published ≤1991 (p=0.02), but not in the remaining RCTs published ≥2005; including only 2/10 FGA-LAI studies. Results in the randomized population were similar to those in the safety/efficacy population.

**Conclusions:** In contrast to naturalistic cohort studies, in RCTs pooled LAIs did not reduce relapse compared to OAPs in patients with schizophrenia.

**Learning Objectives:**
• To understand the data base regarding the relative effectiveness of LAI's in comparison to oral medications in preventing relapse.
• To be able to discuss the methodological challenges in designing clinical trials which can provide generalizable data on this issue.

**Source Of Funding:** The Zucker Hillside Hospital Advanced Center for Intervention and Services Research for the Study of Schizophrenia (MH090590) from the National Institute of Mental Health

**Literature References:**
Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia--a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res. 2011;127(1-3):83-92.
Rosenheck RA, Krystal JH, Lew R, Barnett PG, Fiore L, Valley D, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. N Engl J Med. 2011;364(9):842-51.

## EFFECT OF 12 MONTHS OF TREATMENT WITH LURASIDONE ON WEIGHT IN SUBJECTS WITH SCHIZOPHRENIA

Jonathan M. Meyer, MD[1], Yongcai Mao, PhD[2], Andrei Pikalov, MD, PhD[2], Josephine Cucchiaro, PhD[2], Antony Loebel, MD[2]

[1]University of California, San Diego, CA, [2]Sunovion Pharmaceuticals Inc., Fort Lee, NJ

**Objective:** To evaluate the effect of 12 months of treatment with lurasidone on weight and body mass index (BMI) in subjects with schizophrenia.

**Method:** A post-hoc analysis was performed on pooled observed case (OC) data from 6 clinical studies that evaluated the safety of 12 months of treatment with lurasidone (40-120 mg/day).

**Results:** The analysis sample consisted of 371 subjects who completed 12 months of treatment with lurasidone (mean age at baseline (BL) was 42 years; 67% male). The mean (SD) weight at BL was 74.0 (19.1) kg and the mean (SD) BMI was 25.9 (5.3) kg/m$^2$, with 3.2% of subjects meeting standard BMI criteria for being underweight, 48.8% normal weight, 26.4% overweight, and 21.6% obese. On an OC analysis, the mean (SD) change from baseline in weight was -0.7 kg at 3 months (N=370), -0.6 kg at 6 months (N=360), and -0.7 kg at 12 months (N=347). The mean (SD) change in BMI was -0.3 (1.2) kg/m$^2$ at 3 months, -0.2 (1.7) kg/m$^2$ at 6 months, and -0.2 kg/m$^2$ at 12 months. An increase of ≥7% in weight from BL was observed in 2.7% of subjects at 3 months, 8.6% at 6 months, and 17.6% at 12 months. No dose-response effect for weight change was evident at 12 months in the dosing range of 40 mg to 120 mg (23.4% to 14.1% with ≥7% increase in weight). However, clinically significant weight gain at 12 months was more common in subjects who were normal or underweight at BL (22.8%) compared to subjects who were overweight (11.0%) or obese (12.5%). Overall, 6.3% of subjects shifted, by month 12, from the underweight/normal BMI category to the overweight category, and none from underweight/normal to obese. Conversely, 7.5% of subjects who completed 12 months of treatment and who were overweight at BL shifted from overweight to normal weight by month 12.

**Conclusion:** This pooled analysis demonstrated that 12 months of treatment with lurasidone was associated with a low potential for clinically significant weight gain. No dose-related effect on weight was observed.

**Funded by Sunovion Pharmaceuticals Inc.**

**Learning Objectives:**
- Understand the impact of weight on the long-term health of patients with schizophrenia
- Be knowledgeable about the effect of long-term treatment with lurasidone on weight and BMI

**Source Of Funding:** Funded by Sunovion Pharmaceuticals Inc.

**Literature References:**
- Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry 2007;68(suppl 4):8-13.
- Correll CU et al. Findings of a US national cardiometabolic screening program. Psychiatr Serv 2010;61:892–898.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## IMPACT OF ANTIPSYCHOTIC DRUG ADHERENCE ON THE MANAGEMENT OF SCHIZOPHRENIA AMONG US MEDICARE PATIENTS

Dario Mirski, MD[1], Steve Offord, PhD[1], Bruce Wong, MD[2], Jay Lin, PhD[3], Ross Baker, PhD[4]

[1]Otsuka America Pharmaceutical, Inc., Princeton, NJ, [2]University of Pennsylvania, Philadelphia, PA, [3]Novosys Health, Flemington, NJ, [4]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ

**Background:** Treatment of schizophrenia patients is complicated by drug non-adherence. This study examined the impact of antipsychotic drug adherence on the healthcare usage among Medicare patients with schizophrenia.

**Methods:** Schizophrenic patients, identified by ICD-9 codes from the MarketScan Medicare claims database from 1/1/2005 to 9/30/2010, were required to have >= 12 months of continuous coverage before and after (follow-up) earliest antipsychotic use. Drug adherence was estimated by medication possession ratio (MPR). High adherence (HA) was defined as a follow-up period MPR ≥0.7; a MPR <0.7 indicated low adherence (LA). Follow-up period healthcare usage was assessed.

**Results:** 354 patients were identified, 228 (64%) had LA and 126 (36%) had HA with mean ± standard deviation MPRs of 0.24±0.19 and 0.94±0.09, respectively. LA patients had a greater number of hospitalizations (0.68 vs. 0.44; p=0.02) with a longer length of stay (LOS) (7.0 vs. 2.6 days; p=0.005), more schizophrenia-related inpatient services (18.9% vs. 10.3%; p=0.04) and a greater number of schizophrenia relapse hospitalizations (0.22 vs. 0.11; p=0.03) with significantly longer LOS (3.2 vs. 0.7 days; p=0.03). HA patients had a greater number of pharmacy claims (72.97 vs. 49.54; p<0.001) and use of schizophrenia-related medications (11.13 vs. 4.57; p<0.001). After adjusting for major patient characteristics with Generalized Linear Model, high adherence was associated with fewer any-cause hospitalizations (p<0.001) and shorter LOS (p<0.001).

**Conclusions:** Schizophrenia patients in Medicare have poor adherence to antipsychotics. Patients with low medication adherence vs. high adherence are associated with lower use of schizophrenia-related medication, but more inpatient care and longer LOS.

**Learning Objectives:**

- Poor antipsychotic medication adherence is common among Medicare schizophrenia patients.
- Poor antipsychotic medication adherence is associated with increased healthcare resource usage.

**Source Of Funding:** Otsuka America Pharmaceutical, Inc.

**Literature References:**

- Ascher-Svanum H, Zhu B, Faries DE, Furiak NM, Montgomery W. Medication adherence levels and differential use of mental-health services in the treatment of schizophrenia. BMC Res Notes. 2009;2:6.
- Khaykin E, Eaton WW, Ford DE, Anthony CB, Daumit GL. Health insurance coverage among persons with schizophrenia in the United States. Psychiatr Serv. 2010;61(8):830-4.

## AGE AT ANTIPSYCHOTIC DRUG INITIATION AND HOSPITALIZATION RISK: A US HEALTH CLAIMS DATABASE ANALYSIS

John W Newcomer, M.D.[1], Krithika Rajagopalan, Ph.D.[2], Andrei Pikalov, M.D., Ph.D.[2], Masaaki Ogasa, M.S.[3], Cynthia Siu, Ph.D.[4], Antony Loebel, M.D.[2]

[1]Leonard M. Miller School of Medicine, Miami, FL, [2]Sunovion Pharmaceuticals Inc., Fort Lee, NJ, [3]Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan, [4]Data Power (DP), Inc., Ringoes, NJ

**Objective:** To examine the relationship between age, cardiometabolic abnormalities at onset of antipsychotic treatment and subsequent cardiovascular (CV) or diabetes (DM) related hospitalizations.

**Methods:** Marketscan US claims database from January 2006 through December 2008 was used to investigate hospitalization events, metabolic (Met) and CV comorbidities (identified via ICD-9 diagnosis codes and drug use) in newly treated patients aged < 18 to > 65 with schizophrenia. Eligible patients (N=23,819) had at least 6 months of continuous health plan enrollment before the drug initiation date (index date), and no prescription of any antipsychotic drugs within these 6 months. Survival models were used to estimate the hazard ratio by age-group and gender after controlling for follow-up time (health plan enrollment period).

**Results:** Antipsychotic treatment (prescription length ≥ 3 months) was associated with increased risk for CV/DM related hospitalizations or death (vs. control group, untreated after single prescription of any antipsychotic drug), with the highest hazard ratio observed in the younger age range (treatment-by-age initiation interaction, p<0.001). The hazard for CV/DM related hospitalizations or death was 66% higher than controls for those <18 years, and 51% - 67% higher for those 19-44 years old. In contrast, treated patients aged 55-64 and > 65 had an 11% and 18% lower hazard, respectively, of CV/DM related hospitalizations than controls. Almost all patients with CV/DM related hospitalizations (>97%) had a prior history of Met and CV comorbidities before initiation of antipsychotic drugs. Overall prevalence of Met risk was 41% among new antipsychotic drug users treated for schizophrenia and was age-related (p<0.001). All cause hospitalization was not associated with age at initiation of antipsychotic drug.

**Conclusions:** Our findings indicate that the risk of CV/DM-related hospitalizations in patients with schizophrenia is related to age of antipsychotic drug initiation and the presence of baseline cardiometabolic comorbidities. Increases in risk with treatment initiation underscore the importance of monitoring and management of cardiometabolic risk factors.

**Learning Objectives:**

- To better understand the relationship between age at antipsychotic treatment onset and subsequent hospitalization for cardiometabolic complications.
- Better understand age-related CV risk in newly treated psychiatric patients.

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

**Literature References:**

- Amiel JM; et al.: Addressing cardiometabolic risk during treatment with antipsychotic medications. Curr Opin Psychiatry. 2008; 21:613-8.
- Newcomer JW: Metabolic risk during antipsychotic treatment. Clin Ther. 2004; 26:1936-46.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## NSA-16 REVISITED: IDENTIFYING LATENT FACTORS OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

Danielle Popp, PhD[1], Janet B.W. Williams, PhD[1,2], Elan A. Cohen, PhD[1], Michael J. Detke, MD, PhD[1,3]

[1]MedAvante, Inc., Hamilton, NJ, [2]Columbia University Department of Psychiatry, New York, NY, [3]Indiana University School of Medicine, Indianapolis, IN

**Introduction:** Negative symptoms in schizophrenia are inadequately treated and difficult to assess accurately. The Negative Symptom Assessment (NSA-16) was developed to evaluate the presence and severity of negative symptoms. Previous research suggests a multidimensional structure consisting of five factors: Communication, Emotion/Affect, Social Involvement, Motivation and Retardation. The current study re-examines the multidimensional nature of the NSA-16, when jointly administered with the PANSS, using Confirmatory Factor Analysis (CFA). Interrater reliability and convergent and divergent validity of the NSA-16 are examined.

**Methods:** Blinded independent central raters administered the PANSS and NSA-16 to subjects (n=223) with schizophrenia as part of a randomized clinical trial. Assessments occurred at screening, baseline, and 12 additional visits over one year.

**Results:** The intraclass correlation (ICC) for the NSA-16 total score was .98. Item score ICCs ranged from .72-1.0, indicating high interrater reliability.

A CFA replicating the proposed five factor structure of the NSA was conducted on data from screening visits. Results suggest poor discriminant validity among factors with six between-factor correlations >.90.

Respecification of the model was undertaken by progressively collapsing factors that were highly correlated and examining model fit statistics. A three factor model, collapsing Communication and Social Involvement into a single factor, as well as Emotion/Affect and Retardation, had an acceptable fit (CFI=.85; NFI=.80; RMSEA=.11).

Examination of factor loadings suggested loading the item Reduced Social Drive on the Motivation factor (CFI=.89; NFI=.85; RMSEA=.09).

Finally, to account for variance due to correlated measurement error, error variances for related items were correlated both within and between factors. The resulting modified three factor model with correlated error variance was the best fitting model (CFI=.92; NFI=.87; RMSEA=.08).

The three factors (Communication/Social Involvement, Emotion/Retardation and Motivation) demonstrated convergent validity with the PANSS negative (r=.79, .78 and .54 respectively) and Marder subscales (r=.74, .79 and .54), and divergent validity with the PANSS positive subscale (r=-.23, -.23 and .08).

**Discussion:** Results suggest a three factor multidimensional structure of the NSA-16. Replication of the five-factor structure revealed discriminant validity concerns. Differences in results may be due to the NSA-16 being administered following the PANSS in the current study, which is common in clinical trials. Identifying reliable factors of the NSA-16 is important for developing new treatments to address the multidimensional nature of negative symptoms. Reliance on total scores that treat negative symptoms as unidimensional may obscure the efficacy of treatments on specific domains of negative symptoms and result in failed trials.

**Learning Objectives:**

- Identify the domains of the NSA-16
- Understand the convergent and discriminant validity of the NSA-16

**Source Of Funding:** MedAvante, Inc.

**Literature References:**

- Axelrod, BN, Goldman, RS, Alphs LD. Validation of the 16-item Negative Symptom Assessment. J Psychiat Res 1993; 27(3): 253-258.
- Axelrod, BN, Goldman, RS, Woodard JL, Alphs LD. Factor structure of the Negative Symptom Assessment. Psychiat Res 1994; 52: 173-179.

## EFFICACY AND SAFETY/TOLERABILITY OF 2 APPROACHES FOR SWITCHING TO ILOPERIDONE IN PATIENTS WITH SCHIZOPHRENIA

Peter J. Weiden, MD[1], Gus Alva, MD[2], Matthew Brams, MD[3], Leslie Citrome, MD[4], Ira D. Glick, MD[5], Richard Jackson, MD[6], Greg Mattingly, MD[7], Carrie Guindon[8], Farid Kianifard, PhD[8], Linda Pestreich, MD[8], Adam Winseck, PhD[8], Marla Hochfeld, MD[8]

[1]University of Illinois at Chicago, Chicago, IL, [2]ATP Clinical Research, Costa Mesa, CA, [3]Memorial Park Psychiatry, Houston, TX, [4]New York Medical College, Valhalla, NY, [5]Stanford University School of Medicine, Stanford, CA, [6]Wayne State University, Detroit, MI, [7]Washington University School of Medicine, St. Louis, MO, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ

**Background:** Strategies for switching[1] to iloperidone[2] from other antipsychotic treatments have not been systematically studied. Here we describe results of the multicenter, randomized, open-label i-FANS study.

**Methods:** Subjects were adult (18-64 years) outpatients with a DSM-IV-TR diagnosis of schizophrenia maintained on risperidone, olanzapine, or aripiprazole and experiencing suboptimal efficacy or 1 or more predefined tolerability problems. Patients were randomized 1:1 to switch immediately to iloperidone or to gradually taper their prior antipsychotic dose (to 50% Week 1, 25% Week 2) over the first 2 weeks of iloperidone use. For all subjects, iloperidone was titrated to a target dose of 6 mg bid by Day 4 and could be increased up to 12 mg bid based on investigator judgment. The primary objective was to evaluate these 2 switching approaches, as measured by the Integrated CGI of Change (I-CGI-C) at Week 12. I-CGI-C is a 7-point scale measuring clinician's global impression of the change from baseline in patients' symptoms of schizophrenia and safety/tolerability (eg, 1=very much improved, 4=no change, 7=very much worse).

**Results:** The full analysis and safety sets included 500 subjects (260 randomized to immediate and 240 to gradual switch) and 69.2% completed the study (68.5% in the immediate and 70.0% in the gradual-switch groups). Subjects were (mean±standard deviation) 43.3±11.0 years of age, 56.5% were Black/African American, and 33% were women. Least-squares mean I-CGI-C at Week 12 was 2.837 (improved) for the immediate and 2.826 for the gradual-switch groups (95% CI for delta: -0.232, 0.208). The most common adverse events (AEs) in immediate and gradual-switch groups, respectively, were dizziness (22.3% and 17.5%), dry mouth (20.8% and 17.9%), and somnolence (9.6% and 14.2%). AEs led to discontinuation in 15.0% of subjects in the immediate switch and 10.4% in the gradual-switch groups.

**Conclusions:** Based on I-CGI-C, patients who received iloperidone for 12 weeks after switching from 3 commonly prescribed atypical antipsychotics improved in symptoms and safety/tolerability from the start of treatment, regardless of whether switching was gradual or immediate. AE frequencies were similar between groups; however, more patients discontinued due to AEs in the immediate than in the gradual-switch group.
ClinicalTrials.gov: NCT01207414

**Learning Objectives:**

- Describe reasons for antipsychotic switching in patients with schizophrenia.
- Describe advantages/disadvantages of gradual and immediate switching to iloperidone

**Literature References:**

- Weiden PJ: Switching antipsychotic medications: not enough, too often, or just right? Am J Psychiatry 2011; 168(9):1-3.
- Citrome L: Iloperidone for schizophrenia: a review of the efficacy and safety profile for this newly commercialized second-generation antipsychotic. Int J Clin Pract 2009; 63(8):1237-1248.

**POSTER SESSION 1**
**12:30 P.M. - 2:30 P.M.**

## TRANSDIFFERENTIATION OF MACROPHAGES INTO NEURONAL-LIKE-CELLS AS A POTENTIAL MODEL FOR TREATMENT PREDICTION IN SCHIZOPHRENIA

Alfredo Bellon, MD, PhD [1,2]

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The mechanisms by which antipsychotics elicit a range of therapeutic or undesired effects remain to be fully elucidated. One of the main problems faced when attempting to clarify this dilemma is the impossibility to work with neurons from patients. In order to overcome this obstacle we are transdifferentiating multipotential macrophages obtained from blood circulating monocytes into neuronal-like cells. Recent evidence indicates that a population of monocytes can be differentiated into macrophages with multipotential properties (Zhao et al, *PNAS* 2003;100(5):2426-31; Kuwana et al, *J Leukoc Biol* 2003;74(5):833-45) and in turn transdifferentiated into neuronal-like cells. However, the differentiation rate reported so far is low, and the structure of cells obtained with those protocols do not resemble that of neurons and more importantly do not present electrical activity (Zhao et al, *PNAS* 2003;100(5):2426-31; Kodama et al, *Immunol Cell Biol* 2006;84(2):209-17). We have developed a protocol to transdifferentiate such macrophages into neuronal-like cells that provide differentiation rates of up to 60%. These cells express a wide variety of neuronal markers including Nestin, GAP-43, MAP-2, NeuN, Neurofilament M&H and PSD-95, and most importantly the structure of these neuronal-like cells resembles actual neurons (Figure 1B, C and D). In addition, these macrophage-derived-neuronal-like cells (MDNs) present spontaneous action potentials as well as postsynaptic inhibitory and excitatory currents. To our knowledge this is the first protocol described that allows transdifferentiation of cells obtained from a simple blood sample into neuronal-like cells with electrical activity and without the need to drastically altered the cell's genome. Other models, like induced pluripotent stem cells (iPS cells) rely on altering the cell's genome. In illnesses such as schizophrenia where the genetic load is significant but still not well understood, the impact of drastic genotypic changes cannot be controlled and therefore can become a significant confounder. In order to establish the reliability of our protocol, we have tested it in over 50 individuals (patients and controls included) with consistent differentiation rates determined by structural similarity with neurons and by decreases in expression of CD14 a marker of monocytes/macrophages. Based on data indicating antipsychotics can alter neuronal structure *in vitro* and *in vivo* (Harrison PJ, *Schizophr Res* 1999;40(2):87-99) we aim to use MDNs obtained directly from patients with schizophrenia and controls to determine first if antipsychotics alter its structure and then determine if these structural changes relate to either antipsychotics therapeutic or undesired effects.

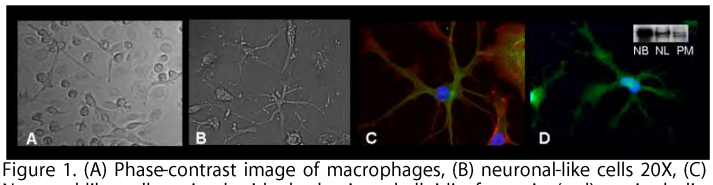


Figure 1. (A) Phase-contrast image of macrophages, (B) neuronal-like cells 20X, (C) Neuronal-like cells stained with rhodamine phalloidin for actin (red), anti-tubulin (green) and DAPI for nucleus (blue) 60X, (D) Neuronal-like cells stained with anti-nestin (green) and DAPI for nucleus (blue) 60X, also WB for nestin detection in neuroblastoma cells (NB), neuronal-like cells (NL) and multipotential macrophages (PM).

**Learning Objectives:**

- Demonstrate that blood cells can be differentiated into neuronal-like cells
- Demonstrate that these neuronal-like cells express neuronal markers, have neuronal like structure and present electrical activity
- Present these neuronal-like cells as a potential model for prediction of treatment outcome in schizophrenia

**Source Of Funding:** FRM (France), University Paris Descartes (France), Young Minds in Psychiatry Award (APA, USA)

**Literature References:**

- Zhao et al, PNAS 2003;100(5):2426-31.
- Kuwana et al, J Leukoc Biol 2003;74(5):833-45.
- Harrison PJ, Schizophr Res 1999;40(2):87-99.

## BAYESIAN MODELING TO PREDICT PLACEBO RESPONDERS IN A SCHIZOPHRENIA TRIAL USING THE POSITIVE AND NEGATIVE SYNDROME (PANSS) SUBSCALE SCORES, IN THE INITIAL WEEKS OF TREATMENT

Christian Yavorsky, PhD [1], Anzalee Khan, PhD [2], Guillermo DiClemente, PhD [1], Mark Opler, PhD [3], Ashleigh DeFries, MS [4], Brian Rothman, PhD [4], Sofija Jovic, PhD [4]

[1]Cronos CCS, Hamilton, NJ, [2]Nathan S. Kline Institute for Psychiatric Research, Wards Island, NY, [3]New York University, New York, NY, [4]ProPhase LLC, New York, NY

**Background:** In schizophrenia there is an appreciable percentage (approximately 40%) of patients in antipsychotic trials who will have a placebo response. In these trials, early changes (within the first weeks) of the PANSS total score are associated with response at end-point (Potkin et al., 2011). Unpredictable placebo response is one of the reasons for clinical trial failure when evaluating antipsychotic treatment.

**Objectives:** To develop a mathematical paradigm of the placebo response in patients with schizophrenia and to assess the relationship between early changes in the PANSS subscale scores (Positive, Negative) and Total Score at different time points (at week 2 and 3) and at endpoint (Week 8).
Methods: The predictive performance of the PANSS subscales and total score at Weeks 2 and 3 is used to identify 'placebo responders' vs. 'placebo non-responders' and its accuracy were assessed using pooled data of four different randomized, double-blind trials of at least 8 weeks duration that compared atypical antipsychotics in the treatment of chronic schizophrenia (N = 809). We used a Bayesian analysis to estimate the expected PANSS subscale scores at week 8 given the PANSS subscale scores at weeks 2 and 3, and then used a Receiver Operating Curve (ROC) analysis to assess the accuracy of the prediction in identifying placebo responder during the early phase of the four trials. Response was defined as a 20% increase from baseline PANSS total score at any time-point after treatment initiation.

**Results:** Descriptive statistics on the fractional change of the PANSS from baseline at weeks 2, 3 and 8 by responders estimate the median % PANSS Positive subscale, Negative subscale and Total Score change gradually increases with time in placebo responders from 0.19, 0.37 and 0.60, respectively, at weeks 2, 3 and 8. While, the median score in the non-responders remains constant over time. The largest separation of responders and non-responders was observed with data collected up to week 3, where the probability curve showed the steepest profile. The comparison between observed and predicted values shows that the median placebo effect at week 8 can be clearly estimated by the longitudinal model using data collected in the initial 2 weeks of treatment, however, the inclusion of data up to week 3 generates an improved estimate of the dispersion of the data around the median effect, closer to the dispersion shown at week 8. Consequently, the Area Under the Curve (AUC) value of 0.81, and 0.83 in the ROC analysis indicates that the fractional PANSS Positive subscale score and PANSS Total Score change at week 3 is a measure of high prognostic utility.

**Conclusions:** The individual PANSS Positive Subscale and Total score at week 8 can be predicted using a Bayesian approach and ROC approach. This analysis indicates that a signal equating placebo responders is linked to the measurement of the fractional change of PANSS Positive subscale and PANSS Total score change from baseline at week 3. This value is 1.8 times larger in placebo responders than in non-responders.

**Learning Objectives:**

- The participant will be able to determine how early changes (within the first weeks) of the PANSS total score are associated with response at end-point?
- The participant will be able to identify unpredictable placebo response as one of the reasons for clinical trial failure when evaluating treatment in schizophrenia?
- The poster will illustrate a novel method to assess signal equating placebo responders is linked to the measurement of the fractional change of psychopathology early on in clinical trials?

**Source Of Funding:** No funding was obtained for this trial

**Literature References:**

- Potkin, S et al., Placebo response trajectories in short-term and long-term antipsychotic trials in schizophrenia, Schizophrenia Research, 2011; 132, 108-113.
- Kemp, AS et al., What is causing the reduced drug placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophrenia Bulletin, 36, 504-509.

POSTER SESSION 1
12:30 P.M. - 2:30 P.M.

## DAYTIME SLEEPINESS AS A MEDIATOR OF TREATMENT OUTCOME IN A PLACEBO- AND QUETIAPINE XR- CONTROLLED TRIAL OF LURASIDONE IN PATIENTS WITH SCHIZOPHRENIA

Henry Nasrallah, MD[1], Robert Silva, PhD[2], Andrei Pikalov, MD, PhD[2], Josephine Cucchiaro, PhD[2], Jane Xu, PhD[2], Cynthia Siu, PhD[3], Antony Loebel, MD[2]

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**Objective:** The impact of daytime sleepiness is under-appreciated, and infrequently assessed using a validated scale. The aim of this post-hoc analysis was to evaluate the effect of fixed doses of lurasidone (80 mg/d or 160 mg/d) and quetiapine XR 600 mg/d on daytime sleepiness and its mediating effects on cognitive and functional outcomes in patients with an acute exacerbation of schizophrenia.

**Methods:** Patients who met DSM-IV criteria for schizophrenia were randomized to 6-weeks of double-blind treatment with lurasidone 80 mg/d (N=125, LUR80), lurasidone 160 mg/d (N=121, LUR160), quetiapine XR 600 mg/d (N=120, QXR), or placebo (PBO, N=122), administered once-daily in the evening after meal. A structural equation model (SEQ) was used to explore potential mediating relationships with cognitive (by CogState computerized battery composite scores) and functional performance (by UPSA-B).

**Results:** QXR was associated with a statistically significant increase in daytime sleepiness (p=0.001, vs. PBO; p<0.001, vs. LUR80; p=0.007, vs. LUR160). Among the 8 common situations assessed in ESS scores, QXR had significant increase in sleepiness in 4 situations (p<0.013, vs. PBO). SEQ models showed a high likelihood that the ESS item "dozing when talking" was a significant mediator of reduction in overall cognitive performance for QXR vs. placebo (p=0.043 US sites), and QXR vs. LUR160 (p=0.006 US sites). The overall ESS total score was not a significant mediator for cognitive outcome. Change in ESS total score was significantly correlated with changes in UPSA-B total score for QXR vs. PBO (p=0.003, US sites), indicating that increase in overall daytime sleepiness mediated reduction in functional capacity for QXR treated subjects, while a reverse trend was observed for those in PBO.

**Conclusion:** In this post-hoc analysis, treatment with 80 mg or 160 mg of lurasidone, administered once-daily in the evening, was associated with a reduction in daytime sleepiness similar to placebo. In contrast, quetiapine XR 600 mg was associated with a significant increase in self-reported daytime sleepiness compared to placebo. Our findings indicate overall daytime sleepiness might be a mediator of change in cognitive performance and performance-based functional outcomes.

**Learning Objectives:**

- To characterize daytime sleepiness in antipsychotic treated patients with schizophrenia, using the Epworth Sleepiness Scale (ESS).
- To evaluate the impact of daytime sleepiness on cognitive and functional performance outcomes.

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

**Literature References:**

- Johns MW: Reliability and Factor Analysis of the Epworth Sleepiness Scale. Sleep 1992; 15:376-381.
- Hawley CJ: Excessive Daytime Sleepiness in Psychiatric Disorders: Prevalence, correlates and clinical significance. Psychiatry Res. 2010:175:138-141.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## RELATIONSHIP OF ADHD SYMPTOM AND GLOBAL SEVERITY ASSESSMENTS IN ADULTS WITH ADHD AND EXECUTIVE FUNCTION DEFICITS TREATED WITH LISDEXAMFETAMINE DIMESYLATE

Thomas Babcock[1], Lenard A. Adler, MD[2], Joel Young, MD[3], Bryan Dirks, MD[1], Patrick Deas, BS[1], Ben Adeyi, MS[1], Richard Weisler, MD[4]

[1]Shire Development Inc., Wayne, PA, [2]New York University School of Medicine and Psychiatry Service, New York VA Harbor Healthcare Syste, New York, NY, [3]Rochester Center for Behavioral Medicine, Rochester Hills, MI, [4]Duke University Medical Center, Raleigh, NC

**Background:** This analysis evaluated the relationship between ADHD-RS-IV scores and CGI-S ratings in adults with ADHD and executive function deficits (EFD) treated with lisdexamfetamine dimesylate (LDX), a prodrug psychostimulant.

**Methods:** Post hoc analysis of a 10-week, randomized, double-blind study in adults with ADHD and clinically significant EFD (baseline Behavior Rating Inventory of EF-Adult Version Global Executive Composite T-scores ≥65) treated with placebo or LDX (30-70 mg/d) examined ADHD-RS-IV total scores for all CGI-S categories. Participants with baseline and endpoint scores were included. No comparative statistics were performed. Safety assessments included adverse events.

**Results:** Active treatment group endpoint CGI-S illness categories of 1=normal, not at all, 2=borderline mentally, 3=mildly, 4=moderately, 5=markedly, and 6=severely ill, and ADHD-RS-IV total scores demonstrated proportionality with mean ADHD-RS-IV total scores of 7.9, 11.9, 18.9, 26.8, 42.0, and 41.5, respectively, though ranges of symptom scores overlapped among CGI-S categories. The safety profile of LDX was consistent with previous studies.

**Conclusions:** ADHD-RS-IV symptom scores appear aligned with CGI-S categories at endpoint in adults with ADHD/EFD. Scale ranges/variance suggest substantial overlap. Thus, assessment of symptoms and global severity are relevant in clinical practice. Small sample size for the CGI-S severe category may explain the nonproportional findings for this category.

**Learning Objectives:**

- Explore the relationship between ADHD symptoms and global illness ratings in adults with ADHD and clinically significant executive dysfunction
- Discuss the importance of multiple approaches to clinical assessment

**Source Of Funding:** Clinical research was funded by the sponsor, Shire Development Inc.

**Literature References:**

- Goodman D, Faraone SV, Adler LA, et al: Interpreting ADHD rating scale scores: linking ADHD rating scale scores and CGI levels in two randomized controlled trials of lisdexamfetamine dimesylate in ADHD. Primary Psychiatry 2010; 17:44-52.
- Weisler R, Dirks B, Deas P, et al: Safety and efficacy of lisdexamfetamine dimesylate in adults with ADHD and self-reported impairments in executive function behaviors. Presented at: AACAP and CAACAP Joint Annual Meeting; October 18-23, 2011; Toronto, Ontario, Canada.

## LISDEXAMFETAMINE DIMESYLATE EFFECTS ON SELF-REPORTED EXECUTIVE FUNCTION AND QUALITY OF LIFE IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: FOCUS ON EMOTIONAL AND SOCIAL DOMAINS

Bryan Dirks, MD, MS[1], Ann C. Childress, MD[2], Richard H. Weisler, MD[3], Patrick Deas, BS[4], Ben Adeyi, MS[5], Lenard A. Adler, MD[6]

[1]Shire Development Inc., Wayne, PA, [2]Center for Psychiatry and Behavioral Medicine, Las Vegas, NV, [3]Duke University Medical Center, Durham, NC, and the University of North Carolina at Chapel Hill, Cha, Raleigh, NC, [4]Shire Development, Wayne, PA, [5]Shire Development Inc, Wayne, PA, [6]New York University School of Medicine and Psychiatry Service, New York VA Harbor Healthcare System, NY, NY

**Objective:** To assess lisdexamfetamine dimesylate (LDX) effects on executive function deficits (EFD) in emotional control (EC) and impaired quality of life (QOL) social domain in adults with attention-deficit/hyperactivity disorder (ADHD) and clinically significant EFD.

**Background:** As assessed by EF behavioral scales, psychostimulant effects on EC and social domains in ADHD are unclear.

**Methods:** This randomized, double-blind, placebo-controlled, 10-wk LDX (30-70mg/d) study enrolled 161 adults (18-55y) with ADHD and EFD (Behavior Rating Inventory of EF-Adult Version [BRIEF-A] Global Executive Composite [GEC] T-score ≥65). Measures of efficacy included self-reported BRIEF-A GEC (primary), indexes/ subscales, and Adult ADHD Impact Module (AIM-A); safety included adverse events and vital signs.

**Results:** At endpoint vs placebo, LDX showed greater numerical improvement on BRIEF-A GEC LS mean (SE) T-score (placebo, −11.1 [1.72]; LDX, −22.3 [1.67]) and Behavioral Regulation and Metacognition indexes. EC subscale scores (least impairment at baseline) significantly improved with LDX vs placebo. AIM-A scale scores (vs placebo) improved significantly with LDX, including the Relationships/Communication scale (least impaired domain). LDX safety profile was consistent with stimulant use.

**Conclusions:** LDX improvements in EF and QOL were observed in all EF subscales and in all AIM-A QOL domains. Interpretation is limited by the short study duration.

**Learning Objectives:**

- Emotional control
- Quality of life social domain

**Source Of Funding:** Clinical research was funded by the sponsor, Shire Development Inc.

**Literature References:**

- Brown TE, Brams M, Gao J, Gasior M, Childress A: Open-label administration of lisdexamfetamine dimesylate improves executive function impairments and symptoms of attention-deficit/hyperactivity disorder in adults. Postgrad Med 2010; 122(5):7-17.
- Weisler R, Dirks B, Deas P, Raychaudhuri A, Dauphin M, Lasser R, Adler L: Safety and efficacy of lisdexamfetamine dimesylate in adults with ADHD and self-reported impairments in executive function behaviors. Poster presented at: AACAP and CACAP Joint Annual Meeting; October 18-23, 2011; Toronto, Ontario, Canada.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## PROFILES OF LISDEXAMFETAMINE AND METHYLPHENIDATE IN RATS TRAINED TO DISCRIMINATE D-AMFETAMINE FROM SALINE

David Heal, PhD[1], Jane Gosden[1], Nigel Slater[1], David Hackett, MS[2]

[1]RenaSci Ltd, Nottingham, United Kingdom, [2]Shire Pharmaceuticals Ltd, Basingstoke, Hampshire, United Kingdom

**Background:** Lisdexamfetamine (LDX; Vyvanse®) is a prodrug that is metabolised to d-amfetamine (d-AMF) exclusively in red blood cells (Pennick 2010, Neuropsychiat Dis Treat 6:317), while methylphenidate (MPH) is a pharmacologically active stimulant. In the USA, both compounds are Schedule 2 Controlled Drugs used to treat ADHD. Studies in drug-experienced human volunteers suggest that the unusual pharmacokinetics of LDX may reduce some aspects of its liability for abuse (Jasinski & Krishnan 2009a,b, J Psychopharmacol 23:410-18 and 419-27).

**Methods:** We have compared the subjective effects of LDX and immediate release MPH (IR-MPH) in groups of 6-9 female rats trained to discriminate d-AMF (0.5mg/kg ip) from saline in a 2-lever operant procedure (generalisation ≥75% responding on the appropriate lever). LDX and IR-MPH were tested by the oral (po) and intraperitoneal (ip) routes.

**Results:** When tested 15min after dosing, LDX (0.5-1.5mg/kg [d-AMF base]) generalised to saline. When tested at 60 min, LDX (0.5-1.5mg/kg po) generalised partially to d-AMF (26-74%) at 0.5-1.0mg/kg and fully (≥75%) at 1.5 mg/kg. At 120min, LDX (0.5 and 0.75mg/kg) generalised to saline and LDX (1.0 and 1.5mg/kg) partially generalised to d-AMF. Fifteen min after po dosing, IR-MPH (3.0-10mg/kg) dose-dependently generalised to d-AMF. Switching to the ip route reduced the time interval required for LDX (0.5-1.5mg/kg) to be recognised as d-AMF-like, but it did not alter the potency of the prodrug. After ip administration, IR-MPH (0.75-3.0mg/kg) dose-dependently generalised to d-AMF, but the dose required for full generalisation decreased from 10mg/kg po to 3.0mg/kg ip.

**Conclusions:** The results show that LDX generalised to d-AMF in rats trained to recognise this discriminative cue. However, LDX's amfetamine-like subjective effects were delayed in onset after po dosing and of relatively short duration. Furthermore, its potency was not increased by switching to the intraperitoneal route. In contrast, generalisation to d-AMF occurred rapidly after oral or intraperitoneal administration of IR-MPH and the potency of the drug was increased 3-fold when dosing was switched to the latter route. The LDX data are consistent with Jasinski's human findings. They also support the hypothesis that the stimulant potential of LDX is lower than that of IR-MPH.

**Learning Objectives:**

- Explore the subjective effects of lisdexamfetamine in rats
- Compare the subjective effects of lisdexamfetamine and methylphenidate

**Source Of Funding:** Shire Pharmaceuticals Ltd

**Literature References:**

- Heal, D., et al. ADHD: Current and Future Therapeutics. Curr Top Behav Neurosci. 2011 Apr 13. [Epub ahead of print].
- Jackson, H., et al. Comparison of the effects of equivalent doses of lisdexamfetamine dimesylate and d-amphetamine on extracellular concentrations of striatal dopamine, locomotor activity and plasma amphetamine concentrations in freely moving rats. 2011; SfN Meeting, Washington Abstract: 775.23.

## A MICRODIALYSIS AND BEHAVIOURAL COMPARISON OF LISDEXAMFETAMINE AND METHYLPHENIDATE IN FREELY-MOVING RATS

Helen Rowley, PhD[1], David Hackett, MS[2], Rajiv Kulkarni, PhD[1], David Heal, PhD[1]

[1]RenaSci Ltd, Nottingham, United Kingdom, [2]Shire Pharmaceuticals Ltd, Basingstoke, Hampshire, United Kingdom

**Background:** Lisdexamfetamine (LDX; Vyvanse®) is a prodrug that is metabolised to d-amfetamine (d-AMF), a stimulant, in red blood cells (Pennick 2010, Neuropsychiat Dis Treat 6:317), while methylphenidate (MPH) is a stimulant. Both compounds are used to treat ADHD.

**Methods:** The Culex Bambino automatically collects samples from dual microdialysis probes and simultaneously measures locomotor activity in freely-moving rats. The effects of LDX (d-AMF base = 0.5, 1.5 and 4.5mg/kg po) and IR-MPH (3, 10 and 30mg/kg po) on locomotor activity and extracellular concentrations of noradrenaline (NA), dopamine (DA) and 5-HT in prefrontal cortex (PFC) and striatum (STR) were compared ≤5hr post-dose. LDX and IR-MPH were tested at pharmacologically equivalent doses based on full generalisation to a d-amphetamine cue in rat drug-discrimination.

**Results:** In PFC, LDX dose-dependently and significantly ($p<0.05$) increased efflux of NA (≤529% of baseline) and DA (≤296%), and at the highest dose, 5-HT (≤284%). IR-MPH increased DA efflux (≤202%) at the low dose and both DA (≤217%; ≤343%) and NA (≤261%; ≤289%) at the mid and high doses; it had no significant effect on 5-HT. In STR, LDX dose-dependently increased extracellular DA (≤364%) and at the high dose, 5-HT (≤359%). IR-MPH (3mg/kg) did not alter DA efflux in STR but it produced small (≤131%) and substantial (≤243%) increases in DA at 10 and 30mg/kg, respectively. IR-MPH (3 or 10mg/kg) did not increase 5-HT in STR. IR-MPH (30mg/kg) only significantly increased 5-HT efflux at one time-point. The actions of LDX and IR-MPH in PFC and STR reached a plateau at 45-60min, but the effects of LDX were larger and more sustained. LDX did not significantly enhance locomotor activity at 0.5mg/kg or 1.5 mg/kg except at two late time-points. A small sustained increase (≤3.6min activity/15min time-bin) was seen at 4.5mg/kg. IR-MPH (10 and 30 mg/kg) significantly increased locomotor activity (≤4.7min/15min).

**Conclusions:** These data show that LDX has larger and more sustained enhancing effects on NA and DA neurotransmission in PFC and STR than IR-MPH. The finding that substantial increases in STR DA can be achieved without causing substantial locomotor activation predict that LDX will have a greater separation between efficacy and stimulant adverse events than IR-MPH.

**Learning Objectives:**

- Determine the effects of lisdexamfetamine on monoaminergic neurotransmission in the prefrontal cortex
- Compare the pharmacological profiles of lisdexamfetamine and methylphenidate

**Source Of Funding:** Shire Pharmaceuticals Ltd

**Literature References:**

- Rowley, H., et al. Simultaneous measurement with hysteresis analyses of the effects of lisdexamfetamine dimesylate and d amphetamine on striatal levels of extracellular dopamine, locomotor activity, and plasma drug concentrations in freely moving rats. Proceedings of the NCDEU Meeting, 2011.
- Heal, D., et al. New perspectives from microdialysis studies in freely-moving, spontaneously hypertensive rats on the pharmacology of drugs for the treatment of ADHD. Pharmacol Biochem Behav. 2008; 90:184-97.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## COMPARING PARTICIPANT-REPORTED MEMORY PROBLEMS WITH MEMORY PERFORMANCE TESTS IN CHRONIC MARIJUANA USERS

Bryan Porterfield, PharmD[1], Scott Goddard, PhD[2], Alan Boyd, BS[3], Kevin Gray, BS, MD[4]

[1]UNC School of Pharmacy, Chapel Hill, NC, [2]Texas A&M University, College Station, TX, [3]CNS Vital Signs, Morrisville, NC, [4]MUSC, Charleston, SC

**Introduction:** The aim of this study was to compare the self-reported memory survey of the Marijuana Problem Scale (MPS), a subjective researcher-administered questionnaire, to a set of memory tests from a computerized neurocognitive testing battery. Data were gathered for this study at baseline before participants were randomized into a marijuana cessation research trial.

**Methods:** Before treatment randomization and during the same baseline study visit, 114 participants completed the MPS per protocol as well as a neurocognitive battery assessing both verbal and visual memory (CNS Vital Signs). Participants' objective neurocognitive memory scores were compared to their MPS scores. ANOVA analysis of the three MPS response groups was performed along with further analysis by a Tukey-Kramer test.

**Results and Discussion:** There were three possible responses to the MPS: no problem = 0, minor problem = 1, and serious problem = 2. Those reporting "no problem," a 0 on the MPS, had a mean verbal memory score of 92.7 with a CI of 84.7 – 100.7 and mean visual memory score of 93.1 with a CI of 88.2 – 98.0. Those reporting memory losses as a "minor problem," a 1 on the MPS, had a mean verbal score of 103.9 with a CI of 99.2 – 108.6 and a mean visual memory score of 102.1 with a CI of 98.6 – 105.7. Those reporting "serious problem," a 2 on the MPS, had a mean verbal memory score of 82.2 with a CI of 65.4 – 99.0 and a mean visual memory score of 91.7 with a CI of 84.5 – 98.9. ANOVA analysis revealed that differences between the verbal and visual memory scores among the 3 MPS groups were significant (p=0.0033 and p=0.0039, respectively).

Further analysis by a Tukey Kramer test showed that certain combinations of groups failed to demonstrate a significant difference in means. Specifically, in verbal memory scores there was a significant difference between those reporting "no problem" and "minor problem" (p=0.0372) and between those reporting "minor problem" and "serious problem" (p=0.0088), but no significant difference between those reporting "no problem" and "serious problem" (p=0.3286). Likewise, in visual memory scores there was a significant difference between those reporting "no problem" and "minor problem" (p=0.0064), but no difference between the other two combinations of groups (p=0.0792 and p=0.9546). These insignificant differences suggest that on the MPS, participants have categorized themselves inconsistently with regard to the objective evidence. It was expected that memory performance would align more consistently with the participant-reported MPS score. Instead, memory impairments reported on the MPS were not commensurate with objective measurements of verbal and visual memory.

**Conclusions:** Participants reported memory impairments differently than what was reflected by scores on objective memory tests. This finding suggests that objective measures of memory may prove more useful than subjective questionnaires, both in the clinic and in research studies in assessing memory impairment.

**Learning Objectives:**

- Describe how chronic marijuana users characterize their memory impairment with a well known scale.
- Describe how chronic marijuana users actually perform on an objective memory tests.

**Source Of Funding:** NIDA grant R01DA026777 and NCRR grant UL1RR029882

**Literature References:**

- Pope HG Jr, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA. 1996 Feb 21; 275(7): 521-7.
- Bolla KI, Brown K, Eldreth D, et al. Dose-related neurocognitive effects of marijuana use. Neurology. 2002 Nov 12; 59(9): 1337-43.
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## THE ALPHA-1 ADRENERGIC ANTAGONIST DOXAZOSIN FOR TREATMENT OF COCAINE DEPENDENCE

Daryl Shorter, MD, Jan Lindsay, PhD, Thomas R Kosten, MD

Houston VAMC/Baylor College of Medicine, Houston, TX

**Background:** Medications decreasing central noradrenergic activity have been associated with attenuation of cocaine effects [1]. In a previous study, our group found that prazosin, an alpha-1 adrenergic antagonist, reduced cocaine-induced reinstatement of drug-seeking behavior in rats [2]. Carvedilol, an antagonist at both alpha-1 and alpha-2 adrenergic receptors, demonstrated an ability to attenuate cocaine effects and reduce cocaine use in humans [3]. Our group selected doxazosin rather than prazosin or carvedilol due to its specificity for the alpha-1 noradrenergic system as well as its longer duration of activity as an alpha-1 blocker.

**Aims:** This pilot study examined the efficacy of doxazosin versus placebo for reducing cocaine use in treatment-seeking cocaine dependent persons.

**Methods:** We screened 42 cocaine dependent subjects and randomized 30 to receive either doxazosin (8mg/day) or placebo for 13 weeks. Participants were titrated on the study medication according to two different schedules (over 3 weeks (DOX-fast) versus 8 weeks (DOX-slow)). All participants also received weekly cognitive behavioral therapy. Urine toxicology was performed thrice weekly and participants completed weekly self-report assessments regarding substance use.

**Results:** Baseline subject characteristics were comparable (88% men, 66% African-American, 100% DSM-IV diagnosis of cocaine dependence, 93% nicotine dependent). Thirty subjects completed the study, including 8 subjects in the DOX-slow group, 9 subjects in the DOX-fast group, and 13 subjects in the placebo group. The total number of cocaine-negative urines was significantly increased in the DOX-fast group. The percentage of total cocaine –negative urines by group were 14% for the DOX-slow group, 45% for the DOX –fast group, and 16% for placebo (chi-square=88, df=2, p<0.0001). The percentage of participants achieving two or more consecutive weeks of abstinence by group was 12% for the DOX-slow group, 55% for the DOX-fast group, and 7% for placebo (chi-square=7.5, df=2, p<0.023).

**Conclusions:** This pilot study suggests the potential efficacy of doxazosin when rapidly titrated in reducing cocaine use.

**Learning Objectives:**

- To review the contribution of the noradrenergic system to the development and perpetuation of the addictive process in cocaine dependence.
- To examine the clinical impact of antagonism of the alpha-1 adrenergic system on cocaine use among cocaine dependent persons.
- To explore how the titration schedule of Doxazosin, an alpha-1 adrenergic antagonist, can affect overall response to the medication in treating cocaine dependence.

**Source Of Funding:** NIH/NIDA 7 P50 DA018197

**Literature References:**

- Petrakis IL, et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. Addiction 2000;95:219-28.
- Zhang XY, et al. Prazosin, an alpha-1 adrenergic antagonist, reduces cocaine-induced reinstatement of drug-seeking. Biological Psychiatry 2005;57:1202-4.
- Sofuoglu M, et al. Carvedilol affects the physiolgical and behavioral response to smoked cocaine in humans. Drug and Alcohol Dependence 2000;60:69-76.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## GENERAL MEDICAL BURDEN IN BIPOLAR DISORDERS: FINDINGS FROM THE LITMUS COMPARATIVE EFFECTIVENESS TRIAL

David E. Kemp, MD, MS[1], Louisa G. Sylvia, PhD[2], Joseph R. Calabrese, MD[1], Andrew A. Nierenberg, MD[2], Michael E. Thase, MD[3], Noreen Reilly-Harrington, PhD[2], Michael J. Ostacher, MD, MS[4], Andrew C. Leon, PhD[5], Terence A. Ketter, MD[4], Edward S. Friedman, MD[6], Charles L. Bowden, MD[7], Michael J. Pencina, PhD[8], Dan V. Iosifescu, MD, MS[9]

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**Introduction:** Patients with bipolar disorder are at increased risk for several general medical conditions, which in concert with other factors may contribute to an up to 30% shorter life expectancy than the general population. Previous studies identified links between cardiometabolic disorders and psychiatric illness severity, suggesting a potential common diathesis for the development of mood symptoms and physical health problems (Kemp et al, 2010). This report examined the prevalence and burden of general medical illnesses and their association with clinical illness features associated with bipolar I or II disorder in a generalizable group of treatment-seeking patients entering the NIMH-sponsored Lithium Treatment Moderate Dose Use Study (LiTMUS) (Sylvia et al, in press).

**Methods:** Data were from the baseline visit of LiTMUS, a comparative effectiveness assessment of moderate doses of lithium as part of optimized personalized treatment (OPT) compared to OPT alone. General medical comorbidity was assessed using the Cumulative Illness Rating Scale (CIRS). Clinically significant high and low medical comorbidity burden were defined as a CIRS total score ≥ 4 and < 4, respectively. We examined the burden of medical comorbidity and its associations with sociodemographic characteristics, clinical features, mood symptoms, pharmacologic treatment, and quality of life.

**Results:** Among 264 participants with sufficient data for analysis, the prevalence of significant medical comorbidity was 53% (n=139). The organ systems most commonly affected were the musculoskeletal/integumentary (33%), respiratory (27%), and endocrinological/metabolic (25%) systems. Migraines (25%), history of head trauma with loss of consciousness (19%), and hypertension (16%) were the individual conditions most commonly reported. Thirty-one percent (n=87) were overweight (body mass index, [BMI] 25-29.9) and 38% (n=105) were obese (BMI ≥ 30), with African-Americans representing the racial group with the highest proportion of stage II obesity (BMI ≥ 35). Patients experiencing a higher burden of medical problems were more likely to present in a current major depressive episode (p=.04), meet criteria for obsessive-compulsive disorder (p=.02), and experience a greater number of depressive and manic/hypomanic episodes over their lifetime (p=0.01), despite a similar age at onset. Participants with high medical comorbidity were also receiving a greater number of psychotropic medications at baseline (p<.001).

**Conclusions:** In this generalizable sample of patients with bipolar I and II disorder, the burden of comorbid medical illnesses is high and appears to influence course of illness and psychotropic medication patterns. These findings highlight the multisystem involvement in bipolar disorder and need for improved understanding of the relationships between psychiatric pathology and medical illness.

**Learning Objectives:**

- To identify the prevalence of medical conditions most commonly affecting patients with bipolar disorder.
- To describe associations between medical comorbidity and clinical illness features in bipolar disorder.

**Source Of Funding:** National Institute of Mental Health, Contract # NO1MH80001

**Literature References:**

- Kemp DE,et al: Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. Bipolar Disord 2010;12:404-13.
- Sylvia LG, et al: Methods to limit attrition in longitudinal comparative effectiveness trials: lessons from the Lithium Treatment - Moderate dose Use Study (LiTMUS) for bipolar disorder.Clin Trials In press.

## DIMINISHED P300 AMPLITUDE IN BIPOLAR MEN WITH A HISTORY OF SUICIDE IN A VISUAL GO/NOGO EVENT RELATED POTENTIAL STUDY

Masoud Kamali, MD[1], Jinsoo Chun, PhD[2], Lisa O'Donnell, LSW[3], Patricia Deldin, PhD[3], Melvin McInnis, MD[1]

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**Introduction:** In the stress-diathesis model of suicide, impulsivity is on a common final pathway to suicidal behavior where thoughts of suicide, in the context of poor impulse control, can culminate in suicidal acts. Impulsivity is a core feature of bipolar disorder (BP), especially during the manic or hypomanic phases of the illness and individuals with bipolar disorder show impairment in many areas associated with impulse control, such as suicidal behavior, substance use or aggression. This study uses the event-related brain potential (ERP) to examine impulse control and its correlation to suicidal behavior in bipolar disorder. We predicted that bipolar patients with a history of suicide attempts will have the smallest amplitude on the P300 component, reflecting problems of impulse control. Here we report preliminary findings from our ongoing study on impulsivity and suicidal behavior in bipolar disorder.

**Methods:** 49 volunteers (female=28) participated in the study, 18 were healthy controls (HC), 31 were individuals diagnosed with BP, 12 had a history of suicide attempts (BPS) and 19 did not (BPNS). EEG measures were collected according to the International 10-20 System, while performing a visual Go/NoGo task. The visual stimuli were presented repeatedly to the left or right visual fields. The P300 component for the Go and NoGo trials were calculated based on a principal component analysis. Peak amplitudes for P300 were subjected to 3 x 2 x 3 x 3 x 2 x 2 repeated-measures ANOVAs with Group (HC, BPNS, BPS) and gender as the between-group factors, and caudality (frontal, central and parietal), laterality (left, midline, and right), condition (Go vs NoGo) and visual field presentation (left and right) as the within-group factors.

**Results:** In the overall analyses, there was a main effect difference for caudality (Wilks' lambda=0.637, P<0.001), laterality (Wilks' lambda=0.439, P<0.001) and condition (Wilks' lambda=0.386, P<0.001) but not visual field (Wilks' lambda=0.992, P=0.552) with the highest P300 amplitude in the central area, on the midline and with the NoGo condition. The main effect for gender was not significant (P=0.361) and the main effect for suicide status did not reach statistical significance (P=0.156). However, there was a statistically significant interaction effect between gender and suicidal behavior status (P=0.031). Follow up analysis showed a significant main effect of suicidal status, but only in men (P=0.018). P300 amplitudes in men, for both BPS (mean=3.199, s.d. =1.100) and BPNS (mean=4.659, s.d.=0.930) were lower compared to HC (mean=7.329, s.d.=0.820) (P=0.008 and P=0.045 respectively).

**Discussion:** A preliminary analysis of our data indicates that male BPS patients show deficits in response inhibition as indicated by lower amplitude on the P300 components of a Go/NoGo test compared to healthy controls. Although BPNS also show lower P300 amplitude, the difference is not as robust. This finding if confirmed in our full sample may be a useful marker for impulsivity and potentially a target for treatment trials.

**Learning Objectives:**

- To recognize the relationship between suicidal behavior and impulsivity
- To consider P300 as a potential marker for impulsivity and suicidal behavior

**Source Of Funding:** MICHR pilot grants (UL1RR024986), AFSP young investigator grant (YIG-XXX-00176-1209) and Prechter Bipolar Research fund

**Literature References:**

- Swann, A. et al. Impulsivity and phase of illness in bipolar disorder. Journal of affective disorders 2003, vol. 73, no. 1-2, pp. 105-111.
- Mann, J. et al. Toward a clinical model of suicidal behavior in psychiatric patients. The American Journal of Psychiatry 1999, vol. 156, no. 2, pp. 181-189.
- Ruchsow, M. et al. Impulsiveness and ERP components in a Go/Nogo task. Journal of neural transmission, vol. 115, no. 6, pp. 909-915.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## SEDATION INTENSITY DURING DOSE ESCALATION OF QUETIAPINE XR OR IR IN BIPOLAR DEPRESSION: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PHASE IV STUDY

Catherine Datto, MD, MS[1], Irina Baldycheva, PhD, MS[1], Robert A. Riesenberg, MD[2]

[1]AstraZeneca Pharmaceuticals LP, Wilmington, DE, [2]Atlanta Center for Medical Research, Atlanta, GA

**Background:** This study hypothesized that the profile of initial tolerability, including somnolence and sedation, differs between quetiapine extended-release (XR) and immediate-release (IR) formulations in patients with bipolar depression.

**Methods:** In a double-blind, double-dummy, randomized, parallel-group study, male or female patients aged 18-50 years with a DSM-IV-TR diagnosis of bipolar I or II depression were randomized, after washout, to receive placebo on Day 1 and quetiapine XR or IR at escalating doses of 50, 100, 200, 300, and 300 mg once daily on the evenings of Days 2-6. Sedation intensity was assessed by self-reported Modified Bond-Lader Visual Analog Scale (VAS) score.

**Results:** Of 139 randomized patients, 134 completed the study. Sedation intensity at 1 hour after the 50 mg dose (the primary study measure) was significantly lower with quetiapine XR than IR (mean [SD] VAS score: 33.4 [26.92] vs 44.0 [31.76]; least-squares mean difference: 12.55, $P$=0.009; modified intent-to-treat population). Sedation intensity was shown in secondary analyses to be significantly lower with quetiapine XR than IR at 1, 2, and 3 hours after each dose on Days 2-6 ($P \leq 0.05$), with similar sedation intensity between treatment groups at 4-14 hours post-dose. Overall tolerability for both formulations was consistent with the known profile of quetiapine.

**Conclusions:** This study demonstrates that, over the initial dose-escalation period, patients with bipolar depression reported significantly lower sedation intensity in the 1-3 hours after taking the quetiapine XR compared to IR formulation.

**Learning Objectives:**

- Review initial tolerability of quetiapine XR in the treatment of bipolar depression
- Compare sedation profiles of quetiapine XR and IR during dose escalation in bipolar depression

**Source Of Funding:** AstraZeneca Pharmaceuticals LP

**Literature References:**

- Datto C, et al. Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release quetiapine fumarate during dose initiation: a randomized, double-blind, crossover study in healthy adult subjects. Clin Ther 2009;31:492-502.
- Suppes T, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J Affect Disord 2010;121:106-115.

## HIGHER OPEN STABILIZATION RATE WITH ADJUNCTIVE ARIPIPRAZOLE IN ACUTE MANIC COMPARED WITH MIXED EPISODES IN BIPOLAR I PATIENTS

Terence Ketter, MD[1], Elizabeth E. Bellocchio, PhD[2], James M. Eudicone, MS[2], Robert A. Forbes, PhD[3], Zia Rahman, PhD[2], Berit X. Carlson, PhD[2]

[1]Stanford University, Stanford, CA, [2]Bristol-Myers Squibb, Plainsboro, NJ, [3]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ

**Background:** In bipolar I disorder (BDI), acute manic compared with mixed episodes are less challenging to treat, with higher monotherapy response and remission rates. [1] Also, lithium compared with valproate monotherapy may yield poorer outcomes in acute mixed vs. manic episodes. This post-hoc analysis of the open stabilization phase of a randomized, double-blind, placebo-controlled, relapse prevention trial[2] assessed adjunctive aripiprazole in manic vs. mixed episodes.

**Method:** BDI patients with current DSM-IV-TR manic or mixed episodes and 2 weeks of inadequate response (Young Mania Rating Scale [YMRS] Total score ≥16 and ≤35% decrease from baseline) to therapeutic levels of lithium or valproate (Phase A), entered an up-to-24-week, open stabilization (YMRS and Montgomery-Asberg Depression Rating Scale [MADRS] Total score ≤12 for 12 consecutive weeks) phase, with adjunctive aripiprazole (Phase B) prior to an up to 52-week randomized, double-blind placebo-controlled relapse prevention phase (Phase C). This analysis focuses on Phase B.

**Results:** In 674 BDI outpatients (395 manic and 279 mixed, 385 taking valproate and 289 taking lithium, mean age 39 years, 59% female), adjunctive aripiprazole yielded ~20% higher open stabilization rates in patients with manic vs. mixed episodes for both those taking valproate (62.4% vs. 42.1%, p<0.0001) and lithium (57.5% vs. 33.9%, p<0.0001). Although open stabilization rates for adjunctive aripiprazole patients taking valproate compared with lithium were higher in both those with manic (5% points) and mixed (8% points) episodes, these differences were not statistically significant. Time to achieve 12 consecutive weeks of stabilization was similar (~125 days) between manic and mixed subjects irrespective of mood stabilizer.

**Conclusions:** Significantly higher stabilization rates with aripiprazole adjunctive to either lithium or valproate were demonstrated in manic patients with BDI as compared with mixed patients, supporting observations from monotherapy studies. Slightly higher stabilization rates in patients with mixed episodes receiving aripiprazole plus valproate vs. lithium suggest possible mitigation with adjunctive aripiprazole of the inferiority of lithium monotherapy to valproate monotherapy in mixed episode patients. Although less mixed patients achieved 12 consecutive weeks of stabilization, adjunctive aripiprazole helped stabilize both manic and mixed patients with similar timing.

**Learning Objectives:**

- Assess open stabilization rates with adjunctive aripiprazole in patients with bipolar I disorder with acute manic and mixed episodes
- Assist clinicians in making treatment decisions for stabilizing patients with acute manic and mixed episodes

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

**Literature References:**

- Bowden CL, et al. Neuropsychopharmacol. 1998;194-199.
- Marcus R, et al. Bipolar Disord. 2011;13:133-144.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## THE EMBLA: AN INNOVATIVE DEVICE FOR MONITORING SLEEP IN BIPOLAR DISORDER

Anna K. Urdahl, BS[1], Louisa G. Sylvia, PhD[1,2], Matt T. Bianchi, MD, PhD[1,2], Leah W. Shesler[1], Stephanie L. McMurrich, PhD[1,2], Andrew A. Nierenberg, MD[1,2], Thilo Deckersbach, PhD[1,2]

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**Introduction:** In bipolar disorder (BD), sleep disturbance is common during and between episodes of depression and mania. However, the relationship between sleep disturbance and mood dysregulation is poorly understood. In part, this is due to due to the lack of comprehensive, objective sleep assessments in patients' natural environment. This study addresses the gaps in sleep methodology and meets two NCDU research aims: 1.) The development of new technologies to advance intervention strategies and 2.) The use of pharmacogenetics, biomarkers, and other means of personalizing interventions.

**Methods:** The Embla device addresses the limitations of current sleep assessments (e.g. self-report, actigraphy, polysomnography) using a novel EKG-based metric that measures autonomic fluctuations to quantify sleep architecture[3-5]. This method is based on the variations in respiratory patterns between wakefulness and sleep and assumes that within sleep, respiration differs not only among stages of sleep, but also between normal and fragmented sleep. The Embla assesses sleep quality by distinguishing stable from unstable sleep based on the novel analytic method of cardio-pulmonary coupling. We pilot tested the acceptability and tolerability of the Embla in participants with BD (N=15). Participants wore the device for seven nights at home before and after a two-session sleep intervention, and wore the device for another seven nights. Mood, self-reported sleep quality, and life functioning were measured at each visit.

**Results:** Data will be presented on the feasibility of using the Embla, the association between self-reported and objective sleep quality and treatment response, and participants' sleep profiles.

**Conclusions:** The Embla is a promising tool to assess sleep and changes in sleep in natural environments.

**Learning Objectives:**

- To test the acceptability and tolerability of the Embla device in participants with BD
- To understand the association between sleep quality, treatment response, and specific sleep profiles.

**Source Of Funding:** None

**Literature References:**

- Plante DT & Winkelman JW. Sleep disturbance in bipolar disorder: Therapeutic implications. Am J.
- Thomas RJ, et al. Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. Sleep. 2007; 30(12):1756-1769.
- Thomas RJ, et al. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. Sleep. 2005; 28(9):1151-1161.
- Thomas RJ, et al. Prevalent hypertension and stroke in the Sleep Heart Health Study: association with an ECG-derived spectrographic marker of cardiopulmonary coupling. Sleep. 2009; 32(7):897-904.

## A NOVEL TOOL FOR TRACKING CHANGES IN PRESCRIBED MEDICATION AND ITS USE IN COMPARATIVE EFFECTIVENESS RESEARCH

Leah W. Shesler, BS[1], Noreen A. Reilly-Harrington, PhD[1,2], Louisa G. Sylvia, PhD[1,2], Anna K. Urdahl, BS[1], Andrew C. Leon, PhD[3], Dan V. Iosifesco, MD[2,4], Michael J. Ostacher, MD[5], Thilo Deckersbach, PhD[1,2], Andrew A. Nierenberg, MD[1,2]

[1]Massachusetts General Hospital, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Weill Cornell Medical College, New York, NY, [4]Mount Sinai School of Medicine, New York, NY, [5]Stanford University School of Medicine, Stanford, CA

**Objective:** Due to the complex nature of psychiatric illnesses, it is generally not feasible to maintain fixed medication and dosing regimens.[1,2] In randomized comparative effectiveness research (CER), medication changes may confound results if one treatment arm requires more medication adjustments to achieve similar outcomes to its comparison group. To our knowledge, a standardized treatment instrument that systematically tracks medication changes is not currently used in CER. We developed the Medication Recommendation Tracking Form (MRTF) to capture study physicians' changes in medication recommendations, and the specific reasons for these changes.

**Methods:** The MRTF was developed as part of the NIMH Lithium Use for Bipolar Disorder (LiTMUS): A Randomized Controlled Effectiveness Trial, a multi-site comparative effectiveness study for bipolar disorder (N=283). The MRTF was created to serve as a proxy for overall effectiveness of the treatments and to monitor physician prescribing behavior. Physicians were trained on the MRTF at the start-up meeting, and conference calls, monitoring visits, and data reports were conducted to ensure compliance. The MRTF was utilized at each study visit, as well as between visits as needed (i.e. unexpected office visit or phone contact) over the six months of the study.

**Results:** We will report data from LiTMUS on the frequency of treatment recommendations as measured by the MRTF. Additionally, we will examine the primary and secondary reasons (i.e. worsening symptoms, intolerable side effects, and patient choice) for medication recommendations by study physicians and their relationship to the type of change recommended.

**Conclusions:** The MRTF is a useful tool for recording changes in medications in CER because it requires physicians to specify reasons for changes in prescribed medications, thereby standardizing the reporting of medication adjustments. The MRTF may also be a useful tool for training new physicians because of the requirement that specific reasons be provided for clinical decisions, and as a method of quality control in psychopharmacology.

**Learning Objectives:**

- Enhancing the methodology of comparative effectiveness research
- Benefits of tracking changes to medication regimens

**Source Of Funding:** NIMH NO1MH8001

**Literature References:**

- 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.
- Trivedi, M.H., et al. Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR*D measurement-based care. Neuropsychopharmacology 2007; 32: 2479-2489.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## SLEEP DISTURBANCE PREDICTS THE FREQUENCY OF CLINICALLY SIGNIFICANT DEPRESSIVE SYMPTOMS IN WOMEN WITH BIPOLAR DISORDER

Erika F.H. Saunders, MD[1,2], Julio Fernandez-Mendoza, PhD[1], Masoud Kamali, MD[2], Scott A. Langenecker, PhD[2], Kelly Ryan, PhD[2], Melvin G. McInnis, MD[2], Alan J. Gelenberg, MD[1]

[1]Penn State College of Medicine, Hershey, PA, [2]University of Michigan, Ann Arbor, MI

**Background:** Women with bipolar disorder (BP) have been reported to have more chronic depressive symptoms than men with BP. Poor sleep quality, which is more prevalent in women, has been shown to correlate with severity of depressive symptoms over time. We hypothesized that there would be gender differences in the relationship between poor sleep quality and depressive symptoms in BP.

**Methods:** 126 women and 61 men with BP were evaluated with the Diagnostic Interview for Genetic Studies, the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Hamilton Depression Rating Scale (HDRS), and the Young Mania Rating Scale (YMRS) at the beginning of the Prechter Longitudinal Study of BP. Every 2 months, depression was re-assessed using the Patient Health Questionnaire (PHQ-9). Variables correlating significantly with PHQ-9 scores at the 6- and 12-month follow-up (FU) were entered in gender-specific linear regression models. The dependent variable (PHQ-9 scores) was analyzed as total scores at 6- and 12-month FU and the frequency of depressive symptoms (the ratio between the number of FUs with clinically significant depressive symptoms (PHQ-9 scores >5) and the total number of FUs obtained for each subject). The independent variables (baseline PSQI and ESS scores), were entered into separate linear regression models. We controlled for age and baseline depression (HDRS) and mania (YMRS) in all models.

**Results:** Depression scores at baseline and at 6- and 12-month FU did not differ between men and women. In women, poor sleep quality predicted the severity of depressive symptoms at both 6- and 12-month FU ($\beta$=.438, p=.0001 and $\beta$=.401, p=.0001, respectively). Also, poor sleep quality predicted the severity of depressive symptoms at both 6- and 12-month FU in men ($\beta$=.355, p=.027 and $\beta$=.464, p=.053, respectively). Importantly, poor sleep quality ($\beta$=.486, p<.0001) predicted the frequency of clinically significant depressive symptoms across FUs in women only. Sleepiness was not associated with depressive symptoms at any of the time points.

**Discussion:** In this sample of BP patients, baseline poor sleep quality was a strong predictor of the frequency of clinically significant depressive symptoms in women, while in men poor sleep quality only predicted the severity of depressive symptoms. Thus, women with BP appear to have a sensitivity to sleep disturbance that affects course of illness. Further studies to investigate the biological underpinnings of the relationship between sleep and mood in women are warranted.

**Learning Objectives:**

- Discuss the relationship between gender and sleep disturbance.
- Discuss the relationship between gender and depressive symptoms in bipolar disorder.

**Source Of Funding:** Internal support

**Literature References:**

- Altshuler LL, Kupka RW, Hellemann G, et al., Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. Am J Psychiatry 2010;167:708-715.
- Baldassano CF, Marangell LB, Gyulai L, et al., Gender differences in bipolar disorder: retrospective data from the first 500 STEP-BD participants. Bipolar disorders 2005;7:465-470.
- Harvey AG, Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. The American Journal of Psychiatry 2008;165:820-829.

## CHANGE IN GLUCOSE AND LIPID METABOLISM USING STABLE ISOTOPE TRACING DURING EUGLYCEMIC CLAMP CONDITIONS DURING INITIAL ANTIPSYCHOTIC TREATMENT FOR DISRUPTIVE BEHAVIOR IN YOUTH

John W. Newcomer, MD[1], Ginger E. Nicol, MD[2,3], Michael D. Yingling, BS[4], Julia A. Schweiger, MD[2], Karen S. Flavin[2], Martha J. Hessler, BS[2]

[1]Miller School of Medicine, University of Miami, Miami, FL, [2]Washington University School of Medicine, St. Louis, MO, [3]Pfizer, Inc, [4]Washington University School of Medicine, St. Louis, MO

**Background:** Rates of prescription of antipsychotic medications in children have increased, 1) largely driven by use for disruptive behavior disorders. 2)The Metabolic Effects of Antipsychotics in Children (MEAC) study (PI Newcomer, MH 072912) characterized the effects of 12 weeks of randomized antipsychotic treat-ment on gold standard measures of adiposity and insulin sensitivity (IS) in antipsychotic-naive children.

**Methods:** Participants (N=97)aged 6-18 with clinically significant aggression and irritability (score of> 18 on Aberrant Child Behavior Checklist Irritability Subscale) and one or more DSM IV diagnoses were randomized to 12 weeks of treatment with aripiprazole, olanzapine or risperidone. Body composition was evaluated with Dual Energy X-ray Absorptiometry (DEXA); whole-body and tissue specific (liver, muscle, adipose) insulin sensitivity were evaluated with a single stage hyperinsulinemic-euglycemic clamp using stable isotopomer tracing. Regression analyses were performed to test the predictive effect of baseline DEXA fat on baseline tissue-specific insulin sensitivity, and the effect of change in DEXA fat over 12 weeks on the change in tissue-specific insulin sensitivity.

**Results:** Pooling treatment groups to test the relationship of baseline and change in adiposity to baseline and change in insulin sensitivity, respectively, the magnitude of increase in adiposity over 12 weeks of antipsychotic treatment were associated with adverse changes in IS at both adipose and hepatic tissues. Specifically, change in DEXA total % fat significantly predicted change in IS at adipose tissue ($F[1,95] = 4.973, p = 0.028$). Baseline relationships between adiposity and tissue-specific IS were also observed.

**Discussion:** Results indicate adverse effects of antipsychotic treatment on body composition, glucose and lipid metabolism. Observed changes in DEXA total % fat predicted reductions in the capacity of insulin to regulate glucose and lipid metabolism. The results suggest a key mechanism by which antipsychotic treatment can increase cardiometabolic risk, underlining the importance of careful attention to the balance of potential risks and benefits of antipsychotic treatment in pediatric populations.

**Learning Objectives:**

- Understand key pathophysiological mechanisms leading to cardiometabolic risk conditions.
- Understand how to interpret changes in cardiometabolic risk in the context of short-term antipsychotic treatment.

**Source Of Funding:** MH72912 P30DK056341

**Literature References:**

- Olfson, Blanco C, Liu L, Moreno C, Laje. Nationaltrends in the outpatient treatment of. children and adolescents with antipsychotic drugs. Arch Gen Psychiary. 2006;63:679-85.
- Cooper WO, Arbogast PG, Ding H, Hickson GB, Fuchs DC, Ray WA. Trends in Prescribing of Antipsychotic Medications for US Children. Ambul Pediatrt. 2006;6(2):79-83.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## THE US AND EU PEDIATRIC INITIATIVES: A RISING OPPORTUNITY FOR PEDIATRIC PSYCHOPHARMACOLOGY

Philippe Auby, MD[1], Jeffrey T. Apter, MD[2]

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**Background:** With the exception of ADHD drugs, only a few psychotropic agents used for psychiatric conditions in children and adolescents have a pediatric indication and a defined posology.

**Methods:** Review of the literature of the development of antidepressant in pediatric Major Depressive Disorder.

- Review of the Pediatric Written Requests (PWR) on the FDA website and Paediatric Investigation Plans (PIP) on the EMA website for Antipsychotic agents.

**Results:** In 2007, the US Pediatric Regulations were amended and reauthorized and the European Authorities launched a new and ambitious pediatric regulation.

Compared to the US, the EU experience in pediatric psychopharmacology research is however less extensive.

Three years after the implementation of the European Paediatric Regulation, a large number of PIPs have been agreed upon and should be implemented in the coming years.

So far, the proportion of paediatric trials as a percentage of all clinical trials has however moderately increased (from 8.2 to 9.4% of all trials).

But, because of the US and EU regulatory requirements, the number of pediatric clinical trials is anticipated to increase. Therefore access to appropriate study patient population will only be possible through worldwide recruitment.

**Conclusions:** Because of the US and EU regulatory requirements, and ongoing pediatric initiatives in Australia, Canada and Japan, the number of pediatric clinical trials is anticipated to increase.

Limitation in appropriate study patient population necessitates recruitment of patients globally.

Ultimately well-conducted research triggered by both US and EU pediatric regulations may bring pediatric populations access to new medications not only in US and EU but indeed globally.

**Learning Objectives:**

- Learn the US and EU pediatric regulation
- Understand the influence of these regulations on pediatric psychopharmacology

**Source Of Funding:** Authors funding

**Literature References:**

- Olski T, et al. Three years of paediatric regulation in the European Union. Eur J Clin Pharmacol (2011) 67:245–252.
- Auby P. Pharmaceutical research in paediatric populations and the new EU Paediatric Legislation: an industry perspective.Child Adolesc Psychiatry Ment Health. 2008 Dec 8;2(1):38.

## SECOND GENERATION ANTIPSYCHOTICS AND RISK OF TYPE 2 DIABETES IN PUBLICLY INSURED CHILDREN AND ADOLESCENTS

Tobias Gerhard, PhD[1,2], William V. Bobo, MD[3], Stephen Crystal, PhD[1], Mark Olfson, MD[4]

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**Background:** Use of second generation antipsychotics (SGAs) in young people has increased substantially despite concerns about adverse cardiometabolic effects. This study aims to characterize new initiators of SGA therapy and to estimate and compare the risk of incident type 2 diabetes for individual SGAs in publicly insured 6 to 24 year-olds.

**Methods:** The study used Medicaid Analytic Extract data from 45 States (2001-2005), representing more than 95% of Medicaid-eligible young people with fee-for-service coverage in the US. We conducted a retrospective cohort study in 161,559 youth newly started on risperidone, quetiapine, olanzapine, aripiprazole, or ziprasidone. New SGA treatment episodes required 365 days of continuous prior Medicaid eligibility without claims for any antipsychotic. Patients were excluded for serious general medical illnesses, pregnancy, polycystic ovarian syndrome or evidence of diabetes mellitus prior to the initiation of the index SGA. Study outcome was incident type 2 diabetes defined by a claims-based algorithm validated against medical records. The positive predictive value of the algorithm was 89.1% and the case definition reliably distinguished between type 1 and type 2 diabetes. Cox proportional hazards models assessed incident risk of type 2 diabetes for individual SGAs compared to risperidone (referent). Follow up began at the date of the first SGA claim and was censored at the occurrence of the study outcome, SGA discontinuation, SGA addition or switch, age 25, end of study period, loss of eligibility or death, whichever came first. Propensity scores (PSs) were used to adjust for a broad collection of claims-based covariates assessed during the 365-day pre-index period. A post hoc analysis assessed corresponding risks among youth with longer term SGA exposures.

**Results:** SGA initiators were predominantly male (64%) with a mean age of 12.6 years. Risperidone was the most commonly initiated SGA (51%), followed by quetiapine (21%), olanzapine (16%), aripiprazole (10%), and ziprasidone (3%). Mean time to censoring was 125 days (median 73 days). Treatment discontinuation was the predominant censoring reason. We observed 289 cases of incident type 2 diabetes during 55,140 person years of follow up for an incidence rate of 5.2/1,000 patients years. Mean time to event was 63 days (median 46 days). PS adjusted models showed no significant differences in type 2 diabetes risk of any SGA compared to risperidone [quetiapine, HR 1.13 (0.81-1.57); olanzapine HR 1.31 (0.93-1.85); aripiprazole HR 1.35 (0.89-2.06); ziprasidone HR 1.44 (0.75-2.79)]. Olanzapine showed an increased risk when analyses were limited to youth with >180 days (HR 2.35, 1.18-4.66) and >365 days (HR 4.74, 1.71-13.14) of follow up.

**Conclusion:** Incidence of type 2 diabetes in our study population greatly exceeded estimates for the general youth population. A majority of cases occurred within less than 2 months of follow up. We observed no significant differences in type 2 diabetes risk between individual SGAs. Short follow up resulting from early SGA discontinuation may have limited our ability to detect such differences. Similarly, failure to detect differences between SGAs may have been a result of residual confounding from channeling of high risk patients to SGAs perceived to have less metabolic adverse effects. Integration of BMI and metabolic laboratory data from electronic medical records with claims data offers an opportunity to address this limitation in future research.

**Learning Objectives:**

- Characterize publically insured youth newly initiated on second generation antipsychotics (SGAs).
- Estimate the comparative risk for incident type 2 diabetes for individual SGAs in publicly insured youth.

**Source Of Funding:** HS017918

**Literature References:**

- Olfson M, et al. National Trends in the Outpatient Treatment of Children and Adolescents with Antipsychotic Drugs. Archives of General Psychiatry 2006;63:679-685.
- Crystal S, et al. Broadened Use of Atypical Antipsychotics: Safety, Effectiveness, and Policy Challenges. Health Affairs 2009;28:770-81.
- Correll C, et al. Cardiometabolic Risk of Second-Generation Antipsychotic Medications During First-time Use in Children and Adolescents. JAMA 2009;302:1765-73.
- The Writing Group for the SEARCH for Diabetes in Youth Study Group. Incidence of Diabetes in Youth in the United States. JAMA 2007;297:2716-2724.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## A COGNITIVE TASK SENSITIVE TO DENTATE GYRUS ACTIVITY WHICH HAS IMPLICATIONS FOR ASSESSING NEUROGENESIS STATUS IN AGING AND VARIOUS CLINICAL CONDITIONS

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**Background:** The seminal discovery that the human dentate gyrus (DG) retains its ability to generate neurons throughout life (Eriksson et al, 1998), has raised the possibility that therapies could be developed to protect or promote this neurogenisis as it deteriorates due to ageing, insult and disease. The DG plays a crucial role in associative memory, and the degenerative changes which compromise neurogenisis in the DG are believed to contribute to memory disturbances in normal ageing and the early stages of AD (Ohm, 2007). Pattern separation has been demonstrated to be under the control of the DG, and fMRI studies have identified the DG to be highly and selectively active when volunteers perform visual object pattern separation tasks, (Kirwan & Stark, 2007). The CDR System picture recognition task assesses visual object pattern separation, and in a cohort of over 3000 volunteers aged 18 to 87 years, a selective, marked and highly significant age-related decline was identified in the ability to discriminate originally presented pictures from different but very similar pictures (Wesnes, 2010). Further, patients with Mild Cognitive Impairment were shown to be selectively inferior on this discrimination compared to age-matched healthy controls. This task thus offers the opportunity to assess DG activity in clinical trials. The aims of the present investigation were (1) to extend these findings by determining whether the time to make these discriminations was also selectively impaired by ageing, (2) to investigate the pattern of changes in children & adolescents from 5 to 17 years, (3) and to investigate whether this discrimination was poorer in clinical populations including late-life depression and oncology.

**Methods:** Data from 47,731 individuals aged 5 to 100 who performed the CDR System picture recognition task on-line were analysed. Data from clinical populations including late life depression and oncology were also evaluated.

**Results:** This study confirmed the original pattern with regard to the decreased ability with adult ageing to discriminate the originally presented pictures from the very similar ones; and extended our knowledge by revealing that younger children were also compromised in this ability. Further, the declining ability to discriminate the pictures with ageing was also associated with selectively longer reaction times, extending our understanding of the phenomenon of declining pattern separation accuracy by showing that it is accompanied by declining speed. Further, other analyses revealed that patients with late-life depression were also found to be selectively impaired on this task, as were oncology patients.

**Discussion:** Neurogenesis in the DG declines with normal ageing, is believed to be compromised in depression and also as a result of chemotherapy in oncology patients. The data from the CDR System picture recognition task are entirely supportive of these patterns. The task provides an opportunity to assess DG activity in various clinical populations, and could be a useful tool in evaluating compounds aimed at promoting, maintaining or restoring neurogenesis. The opportunity to study large populations via the internet has applications to the various long-term patient registries being set up to study preclinical dementia.

**Learning Objectives:**

- Understand the role of neurogenesis in ageing and clinical condtions
- Appreciate how a computerised task can help assess dentate gyrus activity
- Consider the applications for such a task for therapies designed to promote neurogenesis

**Literature References:**

- Eriksson PS Perfilieva E, Björk-Eriksson T et al. Neurogenesis in the adult human hippocampus. Nature Medicine 1998 4: 1313-1317.
- Ohm TG. The dentate gyrus in Alzheimer's disease. Prog Brain Res. 2007 163: 723-740.
- Wesnes KA . Visual object pattern separation: A paradigm for studying the role of the dentate gyrus in memory disorders. Alzheimer's & Dementia 2010 6: Supplement e45.
- Kirwan BC, Stark CEL. Pattern separation processes in the human medial temporal lobe: An fMRI investigation. Learning and Memory 2007 14:625–633.

## SPEECH AS A MARKER OF PRODROMAL HUNTINGTON'S DISEASE

Adam P. Vogel, PhD[1], Andrew Churchyard, MD, PhD[2], Chris Shirbin, BS[2], Julie Stout, PhD[2]

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Huntington's disease (HD), an autosomal-dominant neurodegenerative disorder, is clinically characterized by progressive motor dysfunction, cognitive decline, and psychiatric disturbance with a mean age of onset of 40 years. Speech disturbances (e.g., altered prosody) have been described in symptomatic Huntington's Disease individuals, however, the extent to which speech changes in gene positive pre-manifest (PreHD) individuals is unknown. Here we examine the speech articulation of individuals carrying the mutant HTT gene as a potential objective behavioral/motor/cognitive marker of early HD onset and disease progression.

Speech samples were acquired from 30 individuals carrying the mutant HTT gene (15 PreHD, 15 early stage HD) and 15 matched controls. Participants read a passage, produced a monologue, sustained a vowel and counted from one to 20. Data were analyzed acoustically for measures of timing, frequency, intensity and resonance.

There was a clear effect of group across the majority of acoustic measures, suggesting that speech performance differed in-line with disease progression. Specifically, group comparisons revealed significant differences between the control and the early stage HD group on measures of timing (e.g., speech rate), frequency (e.g., fundamental frequency) and other speech properties across several stimuli.

The speech of early stage HD differed significantly from controls. The speech of PreHD, although not reaching significance, did lie between the performance of controls and early stage HD. This preliminary study suggests that changes in speech production may be developing prior to diagnosis.

**Learning Objectives:**

- Easily elicited speech samples analysed acoustically can provide objective information on disease progression and onset
- Methods for remote monitoring of speech, like the telephone, or basic computing hardware (laptop PC) provide a fantastic opportunity for streamlining data monitoring in this field
- Acoustic analysis of speech is a quantifiable marker of CNS integrity in sleep research.

**Source Of Funding:** National Health & Medical Research Council of Australia (#10012302)

**Literature References:**

- Tabrizi, S.J., et al., Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. The Lancet Neurology, 2009. 8(9): p. 791-801.
- Vogel, A.P., et al., Reliability, Stability, and Sensitivity to Change and Impairment in Acoustic Measures of Timing and Frequency. Journal of Voice, 2011. 25(2): p. 137-149.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## DIFFERENTIAL ASSOCIATION OF COGNITIVE FUNCTION WITH STRESS AND DEPRESSIVE SYMPTOMS BY BDNF VAL66MET GENOTYPE IN PATIENTS WITH CORONARY ARTERY DISEASE

Walter Swardfager, PhD[1,2], Nathan Herrmann, MD[1], Mahwesh Saleem, MS[1], Paul I. Oh, MD[1,2], Paul R. Albert, PhD[3], Krista L. Lanctôt, PhD[1,2]

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**Background:** Patients with coronary artery disease (CAD) show a higher prevalence of depressive symptoms and an increased rate of cognitive decline (Vinkers et al., 2005). Cognitive symptoms, including poorer verbal memory performance and processing speed, are highly prevalent in psychiatric populations; however, few vulnerability factors have been identified. A single nucleotide polymorphism (rs6265; val66met) in the brain derived neurotrophic factor (BDNF) gene has been associated with poorer cognitive function in some populations (Mandelman et al., 2011).

**Methods:** Antidepressant-free patients with CAD entering cardiac rehabilitation were recruited for this study. The val66met BDNF genotype was determined by restriction fragment length polymorphism analysis of buccal swan cell samples. Long delayed verbal recall was assessed using the California Verbal Learning Test, 2nd Ed. (CVLT-II), depressive symptoms were assessed using the Centre for Epidemiological Studies Depression (CES-D) scale and subjective stress was assessed using the Perceived Stress Scale (PSS). Psychomotor processing speed was assessed in a subgroup of patients using the Digit Symbol Coding (DSC) task.

**Results:** Among all patients with CAD (n=90, mean age 65.4±11.5, 86% male), CVLT-II scores were not associated with CES-D scores (r=.007, p=.950) or PSS scores (r=-.076, p=.478); however, in val/met individuals (n=28), both CES-D (r=-.384, p=.044) and PSS scores (r=-.437, p=.020) were associated with poorer CVLT-II scores. Such correlations were not observed in val/val individuals (r=.215, p=.102 and r=.151, p=.256, respectively; n=59). Similarly, in patients assessed with the DSC task (n=52), processing speed was not associated with CES-D or PSS scores in val/val subjects (r=-.110, p=.531 and r=-.237, p=.178, respectively; n=35) but both CES-D scores and PSS scores were associated with poorer processing speed in val/met individuals (r=-.639, p=.010, r=-.647, p=.009, n=15). CVLT-II, DSC, CES-D and PSS scores did not differ between val/val and val/met subjects (p>.05).

**Conclusions:** Associations between cognitive performance and stress and depressive symptoms were identified only in CAD patients carrying the met allele of the val66met BDNF polymorphism. Stratification by BDNF genotype revealed clinically significant psychiatric-cognitive associations that were not apparent in the overall population.

**Learning Objectives:**

- Consider the BDNF genotype as a potential cognitive vulnerability factor.
- Consider stratifying patients by BDNF genotype to reveal cognitive effects that may not be apparent in the overall sample.

**Source Of Funding:** Physicians' Services Incorporated Foundation and the Alzheimer Society Research Program

**Literature References:**

- Vinkers DJ, et al. Generalized atherosclerosis, cognitive decline, and depressive symptoms in old age. Neurology 2005;65(1):107.
- Mandelman SD & Grigorenko EL. BDNF Val66Met and cognition: all, none, or some? A meta-analysis of the genetic association. Genes, Brain and Behavior 2011 doi:10.1111/j.1601-183X.2011.00738.x. [Epub ahead of print].

## REGIONAL PATTERNS IN BASELINE EFFICACY SCALE INTERNAL CONSISTENCY IN AN INTERNATIONAL MDD CLINICAL TRIAL – CAN POOR RATINGS PATTERNS IMPROVE?

Joan Busner, PhD[1], David G. Daniel, MD[2], Stuart A. Montgomery, MD[3], John J. Bartko, PhD[4]

[1]Penn State College of Medicine and Bracket, Wayne, PA, [2]Bracket, Wayne, PA, [3]Imperial College University of London, London, United Kingdom, [4]Biostatistical Consultant, Newville, PA

**Introduction:** Countries with varying levels of research experience increasingly provide data to FDA regulated clinical trials. Failure to separate drug from placebo in MDD trials is a growing, well-documented problem; among many probable contributors, poor ratings practices of efficacy measures are potential threats to study integrity and signal detection. Internal consistency of well-established scales such as the Montgomery Asberg Depression Scale (MADRS) has been used as a proxy measure for raters' correct use of these measures. Improved internal efficacy scale consistency from baseline to endpoint has been demonstrated when raters are monitored by various surveillance methodologies. We assessed a large ongoing international MDD industry-sponsored clinical trial for internal consistency of the primary efficacy scale (MADRS) at baseline and (week 8) endpoint on a per-country basis. All raters were subject to intensive surveillance and local language remediation during the course of the study.

**Method:** Baseline (N=368) and endpoint visit (N=268) MADRS data from an ongoing blinded international industry-sponsored MDD clinical trial were collected via eCRF and subjected to per-country Cronbach's alpha analyses. Raters received remediation and surveillance during the course of the study from clinicians who were unaware of Cronbach's alpha findings.

**Results:** The following countries with at least 10 baseline visits were included: Japan, Finland, Germany, Poland, Russia, Ukraine. Per country baseline mean Cronbach's alphas ranged from very poor (0.07, for Russia) to excellent (0.84, for Ukraine). At endpoint, all values were excellent (ranging from 0.89 to 0.97); the baseline to endpoint change in Cronbach's alpha was statistically significant for each of the 6 countries ($F's = 10.3, 6.9, 4.7, 19.7$, $p's < .0001$ for Russia, Japan, Germany, Poland, respectively; $F's = 7.5, 2.7$, $p's < .05$ for Finland and Ukraine, respectively). Importantly, the most worrisome value at baseline (Russia: 0.07) improved significantly ($p < .001$) to 0.91 at endpoint.

**Discussion:** Baseline internal consistency of the primary efficacy scale, the MADRS, varied dramatically by country and improved significantly and to excellent levels at endpoint visits in this ongoing MDD trial. The study suggests many potentially fruitful areas of additional research including the role of possible baseline inclusion biases, the trajectory of change across study visits, the role of specific remedial contacts, and the relationship of scale internal consistency to regional drug/placebo differences.

**Learning Objectives:**

- Recognize the role regional differences in baseline internal inconsistencies in scoring may play in signal detection in international MDD trials
- Become familiar with a method for detecting baseline internal inconsistencies in scoring in blinded international MDD trials

**Source Of Funding:** Bracket

**Literature References:**

- Khin NA; Chen Y; Yang Y; Yang P; Laughren TP: Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry 2011; 72(4):464–472.
- Busner J; McNamara C; Oakley M; Montgomery SA: Signal detection in adjunctive therapy trials for partially responsive major depressive disorder. Presentation at International Society for CNS Clinical Trials and Methodology (ISCTM), Baltimore, MD, 2010.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## TRAJECTORIES OF SYMPTOM CHANGES IN DEPRESSION CLINICAL TRIALS

Craig Mallinckrodt, PhD [1], Ralitza Gueorguieva, PhD [2], John H. Krystal, MD [3]

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Heterogeneous responses to antidepressant medications and placebo have plagued antidepressant drug development1. The goal of the current study was to use growth mixture models to gain insights into the nature of response to drug and placebo. We reanalyzed data from seven randomized, double-blind, placebo and SSRI-controlled clinical trials of duloxetine (N=2517) to identify distinct trajectories of Hamilton Depression Rating Scale (HAMD) scores during treatment2. In the entire sample and in the antidepressant-treated subsample, we identified trajectories of "responders" (76% of the sample) and "non-responders" (24% of the sample) while placebo-treated subjects were characterized by a single response trajectory. Duloxetine and SSRI did not differ in efficacy and they significantly decreased the odds of following the "non-responder" trajectory compared to placebo. Antidepressant "responders" had significantly better HAMD scores over time than placebo-treated patients, but antidepressant "non-responders" had significantly worse HAMD scores over time than placebo-treated group. This analysis confirmed that the majority of patients treated with serotonergic antidepressants show a clinical trajectory over time that is superior to placebo but it also indicated that a sizable minority of patients do more poorly on these medications than placebo. Medication risks and benefits during serotonergic antidepressant treatment should be carefully controlled. These results should further stimulate the search for biomarkers or other predictors of responder status in guiding antidepressant treatment.

**Learning Objectives:**

- Appreciate the applicability of growth mixture models in understanding patient heterogeneity
- Understand the differential trajectories for drug- and placebo-treated patients

**Source Of Funding:** None

**Literature References:**

- Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R (2008) Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 358: 252-60.
- Gueorguieva R, Mallinckrodt C, Krystal J. (2011) "Trajectories of depression severity in duloxetine clinical trials: insights into placebo and antidepressant responses." Archives of General Psychiatry 68: 1227-1237.

## GAZE BIAS FOR NEGATIVE EMOTION STIMULI AS A MARKER FOR SYMPTOMATIC CHANGE IN DYSPHORIC INDIVIDUALS: A PRELIMINARY METHOD VALIDATION FOR THE EMPIRICAL STUDY OF PLACEBO RESPONSE

Kari R. Nations, PhD, Seth G. Disner, BS, Christopher G. Beevers, PhD

University of Texas, Austin, TX

One of the greatest threats to innovation in the field of psychiatric drug development is the growing placebo response rate in clinical trials (e.g., Walsh, 2002), the magnitude of which is unpredictable and highly compromising to signal detection. Trusted methods for investigating new compounds have not been robust to the industrialization of clinical research, increasing numbers of study participants who seek secondary gain, and declining assessment quality. While meta-analytic research in major depressive disorder (MDD) has uncovered trial design factors that can influence signal detection, including baseline severity and number of treatment arms (Papakostas & Fava, 2009; Fournier et al, 2010), far less work has been devoted to prospectively manipulating expectancy bias and other non-specific elements of treatment in order to better understand their role in placebo response.

A critical challenge to this type of empirical research is that the outcome measures themselves are imprecise. Not only are the scales vulnerable to inflation and inattention, patient-clinician interaction through repeated interview likely increases expectancy bias. Research in this area would ideally control for such factors and rely on a more objective measure of change. However, despite a great deal of effort to identify biomarkers in MDD, the field has not yet arrived at a measure that is both reliable and feasible for most research settings.

Among the more promising surrogate endpoints explored are measures of negative cognitive bias, such as face emotion recognition. Previously conceived as a trait-based marker of depression (Leppanen, 2006), recent data suggest that emotion recognition may also be dependent on mood state, changing with depression remission (Anderson, 2011). Further, there is a growing body of work showing that cognitive biases change with medication treatment (Pringle, 2011) and predict later symptomatic change (Tranter, 2009).

Another measure of cognitive bias uses relatively simple technology to track eye movements upon presentation of emotionally valenced word or picture stimuli. Several studies have shown that depressed and dysphoric individuals, as well as those at risk for future depressive episodes, exhibit eye gaze bias towards sad stimuli (e.g., Gotlib et al, 2004; Koster et al, 2005; Joormann et al, 2007; Beevers et al, 2011). What is not known, however, is whether gaze bias covaries with symptomatic change, and whether it does so in response to or in the absence of pharmacological intervention. We hope that further study will elucidate whether gaze bias represents a viable surrogate for clinical measures in MDD methods research.

Our initial trial will examine gaze bias and symptomatic change in a short-term naturalistic setting. Approximately 80 dysphoric individuals will be recruited from a university subject pool. Cognitive bias will be measured at baseline and two weeks later via gaze tracking and reaction time in a 20-minute word dot probe task. Subjects will complete the Center for Epidemiological Studies Depression Scale (CES-D) at five weekly timepoints. Data will be processed with ASL Results eye tracking software (Applied Science Laboratories, 2010) and analyzed using linear regression models. *We hypothesize that decrease in gaze bias for negative stimuli from baseline to Week 2 will significantly predict symptomatic improvement at Week 5.* Recruitment will begin in February 2012, with interim data presented in Spring.

**Learning Objectives:**

- Methodological challenges in depression treatment outcome research
- Neurocognitive markers for depression symptomatology

**Source Of Funding:** University of Texas seed funds

**Literature References:**

- Koster EHW, et al. Mood-congruent attentional bias in dysphoria: maintained attention to and impaired disengagement from negative information. Emotion 2005; 5: 446-455.
- Gotlib IH, et al. Coherence and Specificity of Information-Processing Biases in Depression and Social Phobia. J Abnorm Psychology 2004; 113, 386.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## RELAPSE RATES IN PSYCHOTIC DEPRESSION ARE LOWER THAN IN NON-PSYCHOTIC DEPRESSION AFTER A SUCCESSFUL COURSE OF ELECTROCONVULSIVE THERAPY (ECT)

Georgios Petrides, MD[1], Rebecca Knapp, PhD[2], Mustafa M. Husain, MD[3], Teresa Rummans, MD[4], Max Fink, MD[5], Martina Mueller, PhD[2], Samuel Bailine, MD[1], Charles H. Kellner, MD[6]

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**Background:** The treatment of patients with psychotic depression presents with different challenges than that of patients with non-psychotic depression. We have previously reported differential response rates to an acute course of Electroconvulsive Therapy (ECT) in psychotic vs. non-psychotic depression. Patients with psychotic depression respond in higher rates and more rapidly than those with non-psychotic depression. In this report, we compare relapse rates of psychotically and non-psychotically depressed patients who responded to an acute course of ECT and were treated with either a fixed course of continuation ECT (C-ECT) or continuation pharmacotherapy (C-PHARM) for six months.

**Methods:** In an NIMH-funded, multicenter, randomized study conducted by the Consortium for Research on ECT (CORE), 531 patients were treated with acute ECT. ECT was administered with bilateral (bifrontotemporal) placement at 1.5 times the seizure threshold. Remission was defined as 2 consecutive ratings of the 24-item Hamilton Rating Scale for Depression (HRSD-24) of 10 or lower. 201 remitters entered a 6-month continuation phase. During that phase, patients were randomized to receive either a fixed course of 10 C-ECT without medications, or the combination of lithium and nortriptyline. No antipsychotics were used in either study arm. We stratified for psychosis status. Relapse was defined as HRSD higher than 17 in two consecutive weekly visits, or hospitalization. We compared relapse rates between psychotic and non-psychotic patients.

**Results:** The intent to treat sample consisted of 184 patients, 66 with psychotic depression and 118 with non-psychotic depression. Demographic characteristics did not differ between the 2 groups.

The six month relapse rates were 28.8% (N=19) among the psychotic patients and 44.9% (N=53) among the non-psychotic (p =0.009).

Among the patients in the C-ECT group, 32.3% of the psychotic patients relapsed, compared to 44.8% of the non-psychotic patients (p=0.159). In the C-PHARM group, the relapse rates were 25.7% and 45% respectively (p=0.22)

Among patients with psychotic depression who received C-ECT, 48.4% remained remitted and among those who received the combination of lithium and nortriptyline, 65.7% remained remitted.

**Discussion:** Relapse rates after a successful course of bilateral ECT are lower in psychotic depression than in non-psychotic depression in a follow-up period of six months.

Relapse rates among patients with psychotic depression are lower in patients receiving the combination of lithium and nortriptyline than in patients receiving continuation ECT without medications on a fixed schedule.
These data support the argument that psychotic and non-psychotic depression represent different nosologic entities and may require different treatment algorithms.

**Learning Objectives:**

- To identify deferrences in relapse rates in psychotic and non-psychotic depression after a successful course of ECT
- To identify differences in relapse rates in psychotically depressed patients after succesful ECT when maintained with either ECT or combination pharmacotherapy

**Source Of Funding:** NIMH, MH-55484, 55486, 55489, 55495

**Literature References:**

- Petrides G, et al., "More Robust Response to ECT in Psychotic Compared to Non-Psychotic Unipolar Depressed Patients: A Report from CORE." Journal of ECT, 17(4): 244-253, 2001.
- Kellner CK, et al., "Continuation ECT versus Pharmacotherapy for Relapse Prevention in Major Depression: a multi-site study from CORE." The Archives of General Psychiatry, 63: 1337-1344, 2006.

## SURVEILLANCE STRATEGIES TO IMPROVE STUDY OUTCOMES IN A DEPRESSION STUDY

Manny Asgharnejad, PhD[1], Steven D. Targum, MD[2], Daniel J. Burch, MD[1], Michael Gibertini, MD[3], Maurizio Fava, MD[4]

[1]CeNeRx, Cary, NC, [2]Clintara LLC, Boston, MA, [3]INC Research, Austin, TX, [4]Massachusetts General Hospital, Boston, MA

**Background:** We introduced several surveillance strategies into a double-blind, placebo-controlled study of an investigational monotherapy medication for treatment resistant patients with Major Depressive Disorder (MDD).

**Methods:** We used: a) Hamilton rating scale for depression (Ham-D) interviews conducted by telephone by site-independent psychiatrists (CTNI-MGH) to confirm depression severity *prior* to randomization in potentially eligible subjects; b) audio-digital pen recordings to allow "dual" site-independent scoring and correlation analyses of site-based interviews of the primary rating measure (MADRS) throughout the entire study; and c) in-study pharmacokinetic analyses to examine medication adherence.

The sponsor carefully chose 31 clinical trial sites in the United States. These sites agreed to and were constantly kept aware of the surveillance methods throughout the study. Most sites had used the pen recording technology in the past and were familiar with the method.

**Results:** Midway through enrollment, there was a high rate of patient completion in the study (80%). Intra-class correlations between site-based and site-independent scores were analyzed throughout the study to confirm rater competency and to identify potential score inflation or ratings discrepancies. There was a significant correlation on the MADRS scores between site-based and site-independent raters at baseline ($r = 0.846$; $p < 0.001$) that got even better after randomization through study endpoint ($r = 0.937$; $p < 0.0001$). Further, pharmacokinetic analyses revealed positive drug levels in 94% of subjects reflecting excellent medication adherence.

**Conclusions:** These preliminary findings suggest that surveillance strategies may reinforce the efforts of clinical trial sites to enroll appropriate subjects, score rating instruments with precision, and foster study and medication compliance in their patients.

**Learning Objectives:**

- To explore alternative site-independent assessment methods in CNS trials
- To compare site-based versus site-independent raters assessment of de-pressed patients
- To understand the manageable factors that may influence CNS trial success

**Literature References:**

- Targum SD, Pollack MH, Fava M. Re-defining Affective disorders: Relevance for Drug Development. CNS Neuroscience and Therapeutics, 14: 2-9, 2008.
- Chandler GM, Targum SD, Pollack M, et al. Validation of Patients for a CNS Trial of Major Depressive Disorder. 49th Annual NCDEU meeting, Hollywood, FL, June 30, 2009.c
- Targum SD, Little JA, Ereshefsky L, et. al. A surveillance strategy to optimize subject selection for CNS trials: "Dual" review using audio-digital recordings. submitted for publication

**Source Of Funding:** CeNeRx

**Literature References:**

- Targum SD, Pollack MH, Fava M. Re-defining Affective disorders: Relevance for Drug Development. CNS Neuroscience and Therapeutics, 14: 2-9, 2008.
- Chandler GM, Targum SD, Pollack M, et al. Validation of Patients for a CNS Trial of Major Depressive Disorder. 49th Annual NCDEU meeting, Hollywood, FL, June 30, 2009.
- Targum SD, Little JA, Ereshefsky L, et. al. A surveillance strategy to optimize subject selection for CNS trials: "Dual" review using audio-digital recordings. submitted for publication.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## LEVOMILNACIPRAN IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: FUNCTIONAL HEALTH AND WELL-BEING EFFICACY RESULTS FROM A PHASE III CLINICAL TRIAL

Steven Blum[1], Stavros Tourkodimitris[1], Adam Ruth, PhD[2]

[1]Forest Research Institute, Jersey City, NJ, [2]Prescott Medical Communications Group, Chicago, IL

**Objective:** Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) in clinical development for the treatment of major depressive disorder (MDD) in adults. Primary and post hoc analyses were conducted on data from a positive Phase III trial (NCT00969709) to evaluate the functional health and well being of patients with MDD treated with sustained released (SR) levomilnacipran.

**Methods:** An 11-week, double-blind, multicenter, parallel-group, placebo-controlled, fixed-dose study in patients (age range, 18-65 years) who met DSM-IV-TR criteria for MDD. Patients had a current major depressive episode ≥8 weeks and a score ≥30 on the Montgomery-Asberg Depression Rating Scale-Clinician Rated (MADRS-CR). Study comprised a 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients were randomized to placebo (PBO; n=175) or once-daily levomilnacipran (LVM; n=529) 40 mg, 80 mg, or 120 mg (titrated-up from an initial dose of 20 mg). Functional health and well being were measured using the SF-36v2 acute (1-week recall) health survey. The SF-36 was scored using norm-based methods that standardize the scores to a mean of 50 and a standard deviation of 10 in the general US population, with higher scores indicative of better health. Changes from baseline to Week 8 in the individual health dimensions [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 computed based on the ITT population. Treatment comparison between LVM and PBO were performed using the least squares mean differences (LSMD) from an ANCOVA model, adjusting for treatment group, pooled study site and baseline value of the underlying score.

**Results:** Patients in both treatment groups had significant deficits in mental-health based on baseline scores for the MCS (PBO: 17.2±9.2; LVM: 18.2±8.5); conversely, baseline scores for the PCS (PBO: 52.6±11.1; LVM: 51.1±11.1) were slightly higher than the population norm. Following 8 weeks of randomized double-blind treatment, patients in the LVM treatment arms compared with PBO-treated patients demonstrated significantly greater improvement in MCS (LSMD = 4.4±1.36; *P*=.0013) and in individual dimensions for GH (2.3±0.69; *P*=.0007), VT (2.4±1.05, *P*=.0228), SF (3.1±1.17; *P*=.0086), RE (3.1±1.20; *P*=.0097) and MH (4.3±1.16; *P*=.0003). Nonsignificant changes were noted for the PCS and the other SF-36 dimension scores (PF, RP, BP).

**Learning Objectives:**

- At the conclusion of this session, participants should be able to evaluate the efficacy of levomilnacipran SR in the treatment of MDD with regard to functional health and well-being.
- At the conclusion of this session, participants should be able to compare physical and mental components of symptom improvement following treatment with levomilnacipran SR in MDD.

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

**Literature References:**

- Ware JE Jr: SF-36 health survey update. Spine 2000; 25:3130-3139.
- Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC: Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry 2007; 62:1217-1227.

## LEVOMILNACIPRAN IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: AN ANALYSIS OF EFFICACY DATA FROM 2 PHASE III STUDIES

Anjana Bose, PhD[1], Carl Gommoll, MS[1], Hua Li, PhD[1], Adam Ruth, PhD[2], Tobie Escher, PhD[1]

[1]Forest Research Institute, Jersy City, NJ, [2]Prescott Medical Communications Group, Chicago, IL

**Objective:** Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with preference for the norepinephrine transporter. Efficacy of levomilnacipran SR in major depressive disorder (MDD) was evaluated using data from recently completed Phase III fixed-dose (Study 1, NCT00969709) and flexible-dose (Study 2, NCT00969150) studies. Statistical superiority on the primary efficacy measure was seen for levomilnacipran SR versus placebo in Study 1 only; other trials are ongoing.

**Methods:** Studies were 11-week, double-blind, multicenter, randomized, placebo-controlled; they comprised a 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients had MADRS-Clinician Rated (MADRS-CR) scores ≥30 with a current major depressive episode ≥8 weeks (Study 1) or ≥4 weeks (Study 2). Patients were randomized to levomilnacipran SR 40, 80, or 120 mg QD or placebo in Study 1 or to levomilnacipran SR 40-120 mg/day QD or placebo in Study 2. Analyses were conducted using pooled data from the 2 studies. Primary efficacy: change from baseline to end of Week 8 in MADRS-CR total score; secondary efficacy: change from baseline to Week 8 in SDS total score; additional efficacy: HAMD-17, CGI-S, and CGI-I. Potential factors leading to variable response pattern in sites common to both studies were explored. Continuous variables were analyzed using a mixed-effects model for repeated measures.

**Results:** Pooled baseline characteristics were similar for placebo (n=358) and levomilnacipran SR (n=712) patients. Significant improvement was seen in the levomilnacipran SR group versus placebo at study endpoint on the MADRS-CR (LSMD=-2.73; *P*=.0009) and SDS (LSMD=-1.44; *P*=.0190). Significant differences at endpoint in favor of levomilnacipran SR were also seen on change in HAMD17 (LSMD=-1.35, *P*=.0175) and CGI-S (LSMD=-0.28, *P*=.0032), and on CGI-I score at Week 8 (*P*=.0040). Significant MADRS-CR improvement was noted in levomilnacipran-treated patients with severe depression defined as MADRS-CR baseline ≥35 (LSMD= -3.31, *P*=.0045) or CGI-S ≥5 (LSMD=-4.22, *P*<.0001). For sites that participated in both studies, similar improvements were seen on MADRS-CR total score for levomilnacipran SR; however, placebo response was higher in Study 2 versus Study 1.

**Conclusion:** Pooled analyses of completed studies showed that levomilnacipran SR- versus placebo-treated patients achieved statistically significant and clinically meaningful improvement in depressive symptoms and functional impairment. Higher placebo response in Study 2 relative to Study 1 may explain the different outcomes in the individual studies.

**Learning Objectives:**

- At the conclusion of this session, participants should be able to evaluate the efficacy of levomilnacipran SR in the treatment of MDD and related functional impairment.
- At the conclusion of this session, participants should be able to should be able to discuss the efficacy of levomilnacipran in different patient subgroups using clinically relevant criteria.

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

**Literature References:**

- Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC: Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry 2007; 62:1217-1227.
- Stahl SM, Grady MM, Moret C, Briley M: SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr 2005; 10:732-747.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## EARLY AND SUSTAINED RESPONSE ACHIEVED ACROSS MULTIPLE MEASURES WITH ADJUNCTIVE ARIPIPRAZOLE IN MDD PATIENTS WITH AN INADEQUATE RESPONSE TO ANTIDEPRESSANT MONOTHERAPY

Daniel E. Casey, MD[1], Kimberly K. Laubmeier, PhD[2], James M. Eudicone, MS[2], Ronald Marcus, MD[3], Robert Berman, MD[3], Ross A. Baker, PhD[4], Jack Sheehan, PhD[2]

[1]Oregon Health and Science University, Portland, OR, [2]Bristol-Myers Squibb, Plainsboro, NJ, [3]Bristol-Myers Squibb, Wallingford, CT, [4]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ

**Objective:** Medications with rapid antidepressant effects address an unmet need in major depressive disorder (MDD), as it can take 6–8 weeks to determine if an antidepressant will help a patient. However, a rapid, transient effect will not improve patients' long-term outcomes. Because of this unmet need, we evaluated the early and sustained antidepressant effects of adjunctive aripiprazole in MDD. Because patients must respond early and at all time points, early and sustained response (ESusR) is a rigorous measure of efficacy. This post-hoc analysis investigated ESusR using measures of symptoms (Montgomery Asberg Depression Rating Scale [MADRS]), total clinical progress from baseline (Clinical Global Impression-Improvement scale [CGI-I]) and clinical state vs. other patients with depression (CGI-Severity scale [CGI-S]).

**Methods:** In this pooled analysis of three similar studies,[1,2] patients had an inadequate response to 1–3 trials of antidepressant therapy (ADT). Each study had an 8-week prospective ADT phase (Phase B), then a 6-week randomized phase of adjunctive aripiprazole vs. adjunctive placebo (Phase C). ESusR was defined as a patient who had a response (≥50% improvement in MADRS total score; CGI-I or CGI-S scores of 1–2 during Phase C) at Week 2 and sustained that response at all subsequent visits (Weeks 3, 4, 5, and 6).

**Results:** The rate of ESusR by MADRS in the adjunctive aripiprazole group was 11.6% (45/387) vs. 5.4% (21/387) in the adjunctive placebo group (p=0.002; relative risk [RR]=2.2, 95% CI: 1.3, 3.5). Rate of ESusR by CGI-I in the adjunctive aripiprazole group was 30.9% (120/389) vs. 15.3% (59/386) in the adjunctive placebo group (p<0.0001; RR=2.0, 95% CI: 1.5, 2.7). For CGI-S, 13.6% (53/390) and 5.1% (20/389) of adjunctive aripiprazole and placebo patients had an ESusR (p<0.0001); RR=2.6, 95% CI: 1.6, 4.3). The mean weekly ending doses at Week 6 of aripiprazole in those with an ESusR by MADRS, CGI-I and CGI-S, respectively, were 8.5, 9.4 and 8.6 mg/d, compared to presumed doses of 11.8, 11.9 and 12.5 mg/d with adjunctive placebo.

**Conclusions:** Adjunctive aripiprazole treatment resulted in ESusR more than twice as often as ADT monotherapy using a symptom scale and two global response measures. These results suggest a response cut-off of MADRS improvement ≥50% is a more rigorous response definition than CGI-I 1–2. For all measures, patients who achieved ESusR received an average dose of 5–10 mg/d, reinforcing the recommended dose in MDD.

**Learning Objectives:**

- Demonstrate the efficacy of adjunctive aripiprazole in inducing early and sustained responses in patients with major depressive disorder
- Assist clinicians in making earlier treatment decisions for their patients

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

**Literature References:**

- Thase ME, et al. Prim Care Companion J Clin Psychiatry. 2008;10:440-447.
- Berman RM, et al. CNS Spectr. 2009;14:197-206.

## SELEGILINE TRANSDERMAL SYSTEM (STS) FOR MAJOR DEPRESSIVE DISORDER (MDD): USE PATTERN, ADHERENCE, AND EFFECT ON HEALTH SERVICE EXPENDITURES

David A. Sclar, PharmD[1], Lawrence J. Cohen, PharmD[1], Kimberly B. Portland, PhD[2]

[1]Washington State University, Spokane, WA, [2]Dey Pharma, LP, Basking Ridge, NJ

**Objective:** There is renewed interest in the use of MAOIs for the treatment of MDD. The selegiline transdermal system (STS) bypasses first pass metabolism, and thereby inhibits MAO in the brain without significantly inhibiting MAO in the gut. The present study was designed to discern: (i) the pattern (sequence) of use of STS in MDD; (ii) level of adherence to STS as compared to alternative antidepressant pharmacotherapy; and (iii) health service expenditures.

**Methods:** This research employed data abstracted from domestic (U.S.) longitudinal archives (Medicaid; Medicare; managed care), cross-sectional surveys (U.S. National Center for Health Statistics), and the published literature. MDD was defined as ICD-9-CM codes 296.2, 296.3, 300.4 or 311. Treatment failure (TF) was defined as receipt of <90 days of antidepressant pharmacotherapy. For longitudinal analyses criterion were: (1) ambulatory patients aged 18 through 75 years; (2) continuous enrollment of 18 months (six months prior to an ICD-9-CM code for MDD (index date); 12 months post index date); (3) no ICD-9-CM code(s) for co-morbid mental illness; (4) initial antidepressant pharmacotherapy: SSRI, SNRI, or STS. Chi-square, multivariate logistic regression, and log-transformed multivariate linear regression were used to assess sequential use of antidepressant pharmacotherapy, predictors of level of adherence, and health service expenditures (intent-to-treat (ITT) and propensity-score basis), respectively. Monte-Carlo simulation (10,000 iterations) was used to further discern and compare 12 month fiscal-risk profiles.

**Results:** For the majority of patients (94%), STS was prescribed as a second or third treatment option for MDD. Specifically, post TF with one SSRI or SNRI (22%); post TF with a second SSRI or SNRI (67%); or post TF with an SSRI or SNRI and augmentation with an atypical antipsychotic (11%). Adjusted for use pattern sequence, STS was associated with a greater probability of receipt of 90 or 180 days of pharmacotherapy (p<0.05). On an ITT or propensity-score basis, use of STS as the last medication prescribed resulted in comparable (p=NS) or reduced (p<0.05) health services expenditures, and greater probability of receipt of 90, or 180 days of pharmacotherapy (p<0.05).

**Conclusion:** Treatment failure is associated with increased health service expenditures. Use of STS post TF (ITT or propensity-score basis) resulted in increased adherence and comparable or reduced health service expenditures.

**Learning Objectives:**

- Understand the extent of treatment failure among patients with major depressive disorder and the associated costs.
- Understand the extent and sequence of use of the selegiline transdermal system among patients with major depressive disorder who have experienced treatment failure.

**Source Of Funding:** Dey Pharma, LP

**Literature References:**

- Thase ME. Treatment-resistant depression: prevalence, risk factors, and treatment strategies. J Clin Psychiatry. 2011;72(5):e18.
- Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. J Clin Psychopharmacol. 2006;26(6):579-86.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## THE EFFICACY OF LEVOMILNACIPRAN IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: RESULTS FROM A PHASE III CLINICAL TRIAL

Carl Gommoll, MS[1], Anjana Bose, PhD[1], Changzheng Chen[1], Adam Ruth, PhD[2], Tobie Escher, PhD[1]

[1]Forest Research Institute, Jersey City, NJ, [2]Prescott Medical Communications Group, Chicago, IL

**Objective:** Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with preference for the norepinephrine transporter. To determine the efficacy of levomilnacipran sustained released (SR) across symptom domains in major depressive disorder (MDD), prospective and post hoc analyses were conducted on a positive fixed-dose Phase III trial (NCT00969709).

**Methods:** An 11-week, double-blind, multicenter, parallel-group, placebo-controlled, fixed-dose study in patients aged 18-65 years who met DSM-IV-TR criteria for MDD. Patients had a current major depressive episode ≥8 weeks and a score ≥30 on the Montgomery-Asberg Depression Rating Scale-Clinician Rated (MADRS-CR). The study comprised a 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients were randomized to placebo or once-daily levomilnacipran SR 40 mg, 80 mg, or 120 mg, initiated at 20-mg and titrated to target dose over 7 days. Primary efficacy: MADRS-CR total score change from baseline to end of Week 8 analyzed using a mixed-effects model for repeated measures (MMRM) approach on the intent-to-treat (ITT) population. Secondary efficacy: Sheehan Disability Scale (SDS) total score change from baseline to Week 8 analyzed using a similar approach. Additional efficacy: $HAMD_{17}$, SF-36, CGI-S, and CGI. Safety and tolerability were evaluated. Post hoc analyses evaluated change from baseline to Week 8 on MADRS-CR single items (MMRM, ITT).

**Results:** The least squares mean difference (LSMD) for MADRS-CR total score change from baseline showed all dose groups were significantly superior to placebo: levomilnacipran SR 40 mg (-3.23, *P*=.0186), 80 mg (-3.99, *P*=.0038), and 120 mg (-4.86, *P*=.0005). On the SDS, significantly greater improvement versus placebo was seen for levomilnacipran SR 80 mg (LSMD, -2.51; *P*<.05) and 120 mg (LSMD,-2.57; *P*<.05). For levomilnacipran SR 80- and 120-mg dose groups, significant improvement relative to placebo was also seen on the $HAMD_{17}$, SF-36, CGI-S, and CGI-I assessments. Improvement across symptom domains was demonstrated by significantly greater decrease in most MADRS-CR single item scores for levomilnacipran SR 80 mg and 120 mg versus placebo (*P*<.05). Levomilnacipran SR was generally well tolerated; however, significantly more patients in the levomilnacipran SR groups discontinued due to AEs (1.7% for placebo and 7.3%, 14.5%, and 6.7%, for levomilnacipran SR 40 mg, 80 mg, and 120 mg, respectively).

**Conclusions:** Levomilnacipran SR 40 mg, 80 mg, and 120 mg demonstrated significant, dose- proportional improvement in depressive symptoms relative to placebo. Post hoc analysis demonstrated superiority for the levomilnacipran 80- and 120-mg doses across symptom domains. Levomilnacipran SR was generally well tolerated; however, significantly more levomilnacipran SR patients discontinued due to AEs.

**Learning Objectives:**

- At the conclusion of this session, participants should be able to evaluate the efficacy of levomilnacipran SR in the treatment of MDD across symptom domains and in relation to functional impairment.
- At the conclusion of this session, participants should be able to evaluate and compare the safety and tolerability profile of 3 different doses of levomilnacipran SR.

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

**Literature References:**

- Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC: Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry 2007; 62):1217-1227.
- Stahl SM, Grady MM, Moret C, Briley M: SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr 2005; 10:732-747.

## EFFICACY AND TOLERABILITY OF VILAZODONE IN PATIENTS WITH MODERATE, MODERATELY SEVERE, AND SEVERE DEPRESSION - POOLED ANALYSES FROM 2 PHASE III TRIALS

Donald S. Robinson, MD[1], Wenjie Song, PhD[2], John Edwards, MD[2], Adam Ruth, PhD[3], Tobie Escher, PhD[2]

[1]Worldwide Drug Development, Burlington, VT, [2]Forest Research Institute, Jersey City, NJ, [3]Prescott Medical Communications Group, Chicago, IL

**Background:** Vilazodone, a serotonin reuptake inhibitor and $5\text{-}HT_{1A}$ receptor partial agonist, is approved by the US Food and Drug Administration for treatment of MDD in adults. The efficacy and tolerability of vilazodone were evaluated across a spectrum of baseline depression severity in post hoc analyses of data from 2 positive, placebo-controlled trials.

**Methods:** Data from the Phase III, 8-week, double-blind, randomized, placebo-controlled trials (NCT00285376, NCT00683592) were pooled to assess the efficacy of vilazodone across a range of depression severity. The trials included patients 18-70 years of age with DSM-IV-TR-defined MDD and a 17-item Hamilton Depression Rating Scale score ≥22. Both trials were of similar design, comprising a 1-week screening period followed by an 8-week double-blind treatment period. Patients randomized to vilazodone were titrated to a target dose of 40 mg, once daily taken with food, over a 2-week period according to a fixed-titration schedule. The primary efficacy outcome (mean change from baseline to Week 8 in Montgomery-Asberg Depression Rating Scale [MADRS] total score) was assessed using an analysis of covariance (ANCOVA) model based on the intent-to-treat (ITT) population with missing values imputed by the last observation carried forward approach. Subgroup analyses stratified patients by baseline depression severity defined by MADRS threshold scores: moderate depression (MADRS<30), moderately severe depression (30≤MADRS<35), and severe depression (MADRS≥35).

**Results:** Of 869 patients (Safety Population), 31% (placebo=143; vilazodone=130) had moderate depression, 49% (placebo=205; vilazodone=220) had moderately severe depression, and 20% (placebo=85; vilazodone=86) had severe depression. In the ITT population, least squares mean difference (LSMD) for change from baseline in MADRS was significantly better for vilazodone relative to placebo in each depression subgroup, with no obvious trend across severity of illness: moderate (LSMD=-2.9; *P* =.0056), moderately severe (LSMD=-2.3; *P*=.0314), and severe (LSMD=-4.1; *P*=.017). The percentages of responders (≥50% MADRS improvement) for vilazodone vs placebo were 41% vs 31% in the moderate (*P*=.0810), 41% vs 29% in the moderately severe (*P*=.0130) and 44% vs 26% in the severely depressed (*P*=.0124) subgroups. Adverse event profiles were similar across severity subgroups.

**Discussion:** Vilazodone treatment compared with placebo showed significantly greater improvement in MADRS in patients with moderate, moderately severe, and severe depression. Mean differences in MADRS change from baseline versus placebo exceeded 2.0 in all 3 groups, treatment effects of clinical significance. The efficacy and tolerability of vilazodone was similar among different depression severity subgroups.

**Learning Objectives:**

- At the conclusion of this session, participants should be able to evaluate the efficacy of vilazodone across the spectrum of depression severity.
- At the conclusion of this session, participants should be able to evaluate how depression severity impacts the tolerability of treatment with vilazodone.

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

**Literature References:**

- Khan A: 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: 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.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## A PILOT STUDY OF ALKS 5461 (BUPRENORPHINE COMBINED WITH ALKS 33) IN TREATMENT RESISTANT DEPRESSION

Maurizio Fava, MD[1], J. Alexander Bodkin, MD[2], Michael Thase, MD[3], Madhukar Trivedi, MD[4], Richard Leigh-Pemberton, MD[5], Yangchun Du, PhD[5], Elliot Ehrich, MD[5]

[1]Massachusetts General Hospital, Boston, MA, [2]McLean Hospital, Belmont, MA, [3]University of Pennsylvania, Philadelphia, PA, [4]UT Southwestern Medical Center, Dallas, TX, [5]Alkermes PLC, Waltham, MA

**Background:** Opioids appear to have a role in mood regulation, however, their use in depression has been traditionally limited by abuse potential. ALKS 5461 consists of buprenorphine (BUP) combined with ALKS 33, a sublingually bioavailable mu opioid antagonist. This study provided an initial assessment of safety and efficacy of ALKS 5461 in treatment resistant depression (TRD). Two dose ratios of BUP: ALKS 33 were evaluated- an 8:1 ratio associated with partial blockade and a 1:1 ratio with complete blockade of BUP mu agonist effects.

**Methods:** In this double-blind study, 32 patients with TRD were randomized (1:6) in 2 cohorts to a daily sublingual dose of placebo or ALKS 5461. The 8:1 ratio cohort was treated with escalating doses of 2:0.25mg/4:0.5mg for 7 days. The 1:1 ratio cohort received escalating doses of 4:4mg/8:8mg. Efficacy was measured using the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and the Montgomery-Åsberg Depression Rating Scale (MADRS). Visual analog scales assessed drug liking and subjective drug effects.

**Results:** Changes from baseline to day 7 in HAM-D-17 scores were -1.0 (4.2), -5.0 (6.1), and -6.7 (3.4), [mean (SD), placebo, 8:1 ratio, and 1:1 ratio; p=0.032 for 1:1 ratio vs. placebo]; changes in MADRS scores were -3.5 (5.8), -8.5 (7.4), and -11.4 (6.6), respectively (p=0.054 for 1:1 ratio vs. placebo). Patients receiving the 8:1 ratio experienced greater subjective scores of "Feeling High" and "Feeling Sedated" compared to the 1:1 ratio. The most common AEs were dizziness, nausea, vomiting, and sedation, which occurred most frequently at the 8:1 ratio.

**Conclusions:** ALKS 5461 was safe and generally well tolerated. Evidence of rapid efficacy was observed with both dose ratios at 7 days, with greatest efficacy at the 1:1 ratio, i.e. with complete mu blockade. More favorable safety and subjective drug effect profiles were observed for the 1:1 ratio. ALKS 5461 may represent a novel treatment of TRD with a rapid onset of effect.

**Learning Objectives:**

- Understand the therapeutic potential of combining two mu opioid receptor modulators for treatment resistant depression
- Understand the treatment implications of combining ALKS 33 and BUP at different dose ratios

**Source Of Funding:** Alkermes PLC

**Literature References:**

- Bodkin JA, et al. Buprenorphine treatment of refractory depression. J Clin Psychopharmacol 1995; 15:49-57.
- Nyhuis PW, et al. Opiate treatment in depression refractory to antidepressants and electroconvulsive therapy. J Clin Psychopharmacol 2008; 28:593-595.

## THE CLINICAL IMPACT OF AN ANTIDEPRESSANT PHARMACOGENOMIC ALGORITHM

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[1]Pine Rest Christian Mental Health Services, Grand Rapids, MI, [2]Michigan State University College of Human Medicine, Grand Rapids, MI

**Background:** Genes linked to metabolism (CYP450 2D6, 2C19, and 1A2), efficacy (SLC6A4), and tolerability (5HTR2A) of antidepressants may inform treatment selection. Published case reports suggest that pharmacogenomic (PGx) testing may improve outcomes in drug treatment of depression. This prospective randomized double-blind pilot study evaluated the clinical impact of a 5-gene PGx algorithm and interpretive report on antidepressant selection and treatment outcomes in depressed outpatients.

**Methods:** Depressed adult outpatients were randomized to a PGx-testing (PGxT, n = 25) or treatment as usual (TAU, n = 24) arm. Depression severity and medication side effects were assessed at baseline and 2, 4, and 8 weeks after a routine clinic visit using the HAM-D and the Frequency, Intensity, and Burden of Side Effects Rating Scale (FIBSER), respectively. Treating clinician use of the report was optional. Study subjects and their raters were blinded to treatment arm. Treating clinicians were surveyed regarding the influence of PGxT on antidepressant selection.

**Results:** Subjects in the PGxT arm had a greater decrease in HAM-D mean change scores from baseline than subjects in the TAU arm at week 4 (p =0.029) but not at weeks 2 and 8 (p=0.22 and p=0.27). Thirteen PGxT vs 6 TAU subjects were responders (p=0.055) and 8 PGxT vs 1 TAU subject were remitters during the study (p=0.012). No difference in side effect burden was detected between treatment arms. The PGx report had a high/moderate and low/no level of influence on treatment decisions in 15 (60%) and 10 (40%) PGxT subjects, respectively.

**Conclusions:** This is the first prospective randomized study designed to evaluate the impact of PGx testing on antidepressant treatment. Though patient group sizes were small, and application of the PGx test was uncontrolled, clinical improvement was found, and a greater number of PGxT subjects remitted vs TAU subjects. Treatment decisions were highly or moderately influenced by the PGx report in a majority of PGxT subjects. An additional prospective, double-blind, TAU-controlled clinical study of PGx testing is warranted to evaluate its effect on response and remission during antidepressant therapy.

**Learning Objectives:**

- Describe the impact of PGx testing on treatment outcomes in depressed outpatients.
- Characterize the influence of PGx testing on antidepressant selection.

**Source Of Funding:** AssureRx Health, Priority Health, Pine Rest Foundation

**Literature References:**

- Black J, et al. The impact of CYP allelic variation on antidepressant metabolism: a review. Expert Opin. Drug Metab. Toxicol. 2007; 3:21-31.
- Serretti A, et al. Meta-analysis of serotonin transporter gene promoter polymorphism association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry 2007;12:247-257.
- Murphy G, et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003; 160:1830-1835.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## RELATIONSHIPS BETWEEN GABA LEVELS AND FUNCTIONAL CONNECTIVITY ARE DISRUPTED IN ADOLESCENT MAJOR DEPRESSIVE DISORDER

Vilma Gabbay, MD, MS[1,2], Benjamin A. Ely, BS[1], Chuqing Kang[1], Barbara J. Coffey, MD, MS[1,2], Francisco X. Castellanos, MD[1,2], Dikoma C. Shungu, PhD[3], Michael P. Milham, MD, PhD[2,4]

[1]New York University Child Study Center, New York, NY, [2]Nathan S. Kline Institute, Orangeburg, NY, [3]Weill Cornell Medical College, New York, NY, [4]Child Mind Institute, New York, NY

**Background:** Adolescent major depression (MDD) is a significant public health concern associated with functional and structural abnormalities in the striatum[1] and anterior cingulate cortex (ACC).[2] We recently demonstrated that ACC levels of gamma-aminobutyric acid (GABA) are decreased in adolescents with MDD.[2] Here, we extend these findings by examining the relationship between ACC GABA levels and striatal functional connectivity (FC) in adolescents with MDD and healthy controls (HC). We hypothesized that the ACC GABAergic system modulates fronto-striatal FC, and that this modulation is disrupted in adolescents with MDD.

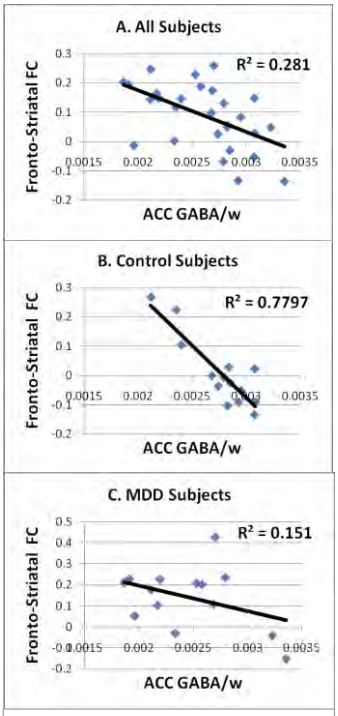


**Fig. 1:** Correlation of ACC GABA levels and FC between the left ventral caudate seed and the anterior frontal cortex for [A] all subjects, [B] control subjects, and [C] MDD subjects.

**Methods:** Patient Population consisted of 18 MDD and 15 HC subjects, ages 12-19. Subjects diagnosed with MDD via the K-SADS-PL had episode duration ≥ 6 weeks and CDRS-R scores ≥ 40. All subjects were psychotropic medication-free for > 3 months.

FC Measurements by fMRI for 6 bilateral striatal seeds were obtained on a 3.0 T scanner by acquiring 197 contiguous echo planar imaging functional volumes (TR = 2s, 39 slices) during rest with eyes open. A high-resolution $T_1$-weighted 3D anatomical image was also acquired using a magnetization prepared gradient echo sequence for spatial normalization and localization.

*In Vivo* GABA Measurements by $^1$H MRS were acquired from a single 2.5x2.5x3.0 cm$^3$ ACC voxel using a GE 3.0T "EXCITE" MR system and an 8-channel phased-array head coil via the standard J-editing difference method. Rank-based ANCOVA compared the MDD and HC groups while adjusting for age, handedness, sex, and ethnicity.

**Results:** In the combined group of MDD and HC subjects, fronto-striatal FC was inversely correlated with ACC GABA concentrations ($R^2$ = 0.28, Fig. 1A). In keeping with our hypothesis, this correlation was much stronger for the HC group ($R^2$ = 0.78, Fig. 1B) than for the MDD group ($R^2$ = 0.15, Fig. 1C).

**Conclusions:** Our findings are in line with previously published reports of ACC and striatal metabolic and functional abnormalities in MDD, and are potentially consistent with the ACC GABAergic system modulating fronto-striatal FC. These findings suggest that FC and GABA levels could serve as objective imaging biomarkers of MDD as well as targets for treatment and response monitoring.

**Learning Objectives:**

- To understand the alterations in fronto-striatal FC and ACC GABA levels associated with adolescent MDD.
- To understand how combining distinct research modalities can lead to novel discoveries in neuropsychiatric investigations.

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

**Literature References:**

- Forbes EE, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry. 2009 Jan;166(1):64-73.
- Gabbay V, et al. Anterior Cingulate Cortex Gamma-Aminobutyric Acid in Depressed Adolescents: Relationship to Anhedonia. Arch Gen Psychiatry. In press.

## LEVOMILNACIPRAN IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: AN ANALYSIS OF SAFETY AND TOLERABILITY DATA FROM 2 RANDOMIZED PLACEBO-CONTROLLED TRIALS

William Greenberg, MD[1], Hua Li, PhD[1], Carl Gommoll, MS[1], Adam Ruth, PhD[2], Tobie Escher, PhD[1]

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**Objective:** Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with preference for the norepinephrine transporter. Safety and tolerability of levomilnacipran SR in major depressive disorder (MDD) were evaluated using data from recently completed Phase III fixed-dose (Study 1, NCT00969709) and flexible-dose (Study 2, NCT00969150) studies. Statistical superiority on the primary efficacy measure was seen for levomilnacipran SR versus placebo in Study 1 only; other trials are ongoing.

**Methods:** Studies were 11-week, double-blind, multicenter, randomized, placebo-controlled; they comprised a 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients had MADRS-Clinician Rated (MADRS-CR) scores ≥30 with a current major depressive episode ≥8 weeks (Study 1) or ≥4 weeks (Study 2). Patients were randomized to levomilnacipran SR 40, 80, or 120 mg QD or placebo in Study 1 or to levomilnacipran SR 40-120 mg/day QD or placebo in Study 2. Analyses were conducted using pooled data from the 2 studies. Safety and tolerability evaluations included adverse events (AEs), laboratory measures/vital signs, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

**Results:** Baseline characteristics were similar for placebo (n=358) and levomilnacipran SR (n=712) groups. Overall, 80.2% of placebo and 70.6% of levomilnacipran SR patients completed the study; 84.1% of placebo and 73.5% of levomilnacipran SR patients were exposed to study drug for ≥6 weeks. During 8-week double-blind treatment, 1 placebo (0.3%) and 3 levomilnacipran SR patients (0.4%) had serious AEs (SAEs); 1 SAE (aggression) in a levomilnacipran SR patient was considered related to drug. Discontinuation due to AEs occurred in 2.0% of placebo and 9.1% of levomilnacipran SR patients. During double-blind treatment, 63.1% of placebo and 78.8% of levomilnacipran SR patients reported a treatment-emergent AE (TEAE). The majority of TEAEs were transient and mild to moderate in intensity. The most common (≥10%) TEAEs (levomilnacipran vs placebo) were headache (12% vs 17%), nausea (3% vs 16%), and dry mouth (8% vs 10%); median time to onset and mean duration of these AEs were similar between placebo and levomilnacipran SR. Potentially clinically significant (PCS) changes in blood pressure/pulse were seen in 0.3%/0.8% of placebo and 0.1%/0.1% of levomilnacipran SR patients. PCS weight changes (≥7% increase/decrease) occurred in 1.1%/0.6% placebo and 0.7%/1.8% of levomilnacipran SR patients. C-SSRS–rated suicidal ideation was reported in 27% of placebo and levomilnacipran SR patients; suicidal behavior was reported in 0.3% of placebo and 0.6% of levomilnacipran SR patients.

**Conclusion:** Safety data from 2 double-blind trials suggests that levomilnacipran SR was generally well tolerated. Most TEAEs were transient and mild-moderate intensity.

**Learning Objectives:**

- At the conclusion of this session, participants should be able to evaluate the adverse event profile of levomilnacipran SR in the treatment of MDD based on results from a pooled analysis of double-blind, placebo-controlled data.
- At the conclusion of this session, participants should be able to discuss the tolerability of levomilnacipran SR as it relates to adverse events, discontinuation due to adverse events, and clinical laboratory measures.

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

**Literature References:**

- Stahl SM, Grady MM, Moret C, Briley M: SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr 2005; 10:732-747.
- Schatzberg AF: Safety and tolerability of antidepressants: weighing the impact on treatment decisions. J Clin Psychiatry 2007; 68(Suppl 8):26-34.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## EFFECTS OF CITALOPRAM AND ESCITALOPRAM ON FMRI RESPONSE TO AFFECTIVE STIMULI IN HEALTHY VOLUNTEERS SELECTED BY 5-HTTLPR GENOTYPE

Michael E. Henry, MD[1,2], Tara L. Lauriat, PhD[1,2], Steven B. Lowen, PhD[2], Jeffrey H. Churchill[1], Colin A. Hodgkinson, PhD[3], David Goldman, MD[3]

[1]Steward St. Elizabeth's Medical Center, Boston, MA, [2]McLean Hospital, Belmont, MA, [3]National Institute on Alcohol Abuse and Alcoholism, Rockville, MD

**Introduction:** Pharmaco-fMRI is emerging as a popular strategy for investigating the effects of candidate psychotropics on central nervous system activity. In order to be useful for this purpose, it is important to establish the sensitivity of this approach. Citalopram has been approved as an antidepressant in both its racemic and S enantiomer forms. In addition, there is evidence that the R enantiomer of citalopram has antagonist properties. We therefore hypothesized that the effects of an equal dose of S-citalopram, given as racemate, would be different from those of pure S-citalopram on the brains of healthy volunteers as detected by fMRI.

**Methods:** Healthy male volunteers who did not have a low expression genotype for the serotonin transporter (SS or SLg), were recruited for a double-blind, crossover trial of escitalopram, citalopram, and placebo followed by functional magnetic resonance scanning. Doses were one week of 10 mg followed by one week of 20 mg for escitalopram, one week of 20 mg followed by one week of 40 mg for citalopram, and 2 weeks of placebo. Scans were obtained on the last day of each dosing period. Stimuli included happy and fearful faces presented in overt, covert, and rapid covert presentations as well as affective words. Of the 27 subjects randomized, 11 had complete data for analysis.

**Results:** Significant task-related activation and medication effects were observed in regions with known roles in face processing. These regions include the fusiform gyrus, lingual gyrus, and lateral inferior occipital gyrus. The affective face stimuli alone activated the superior frontal cortex when displayed in a covert masked presentation, with a greater response to happy faces than fearful faces. Differences between citalopram and escitalopram were observed in the insula, which is involved in face processing and interoception.

**Conclusions:** These findings suggest that pharmaco-fMRI is sufficiently sensitive to detect differences between racemic citalopram and its S enatiomer, when dosed to deliver equal amounts of S-citalopram. The limited sample size and the use of healthy volunteers instead of depressed patients may have limited the number and size of brain regions showing a difference. Further study with a larger sample size and psychotropic medications that work through different mechanisms would be helpful in determining the utility of these methods.

**Learning Objectives:**

- The participants will be able to describe fMRI responses to affective stimuli following antidepressant administration.
- The participants will be able to discriminate between fMRI responses to citalopram and escitalopram.

**Source Of Funding:** Forest Research Institute

**Literature References:**

- Windischberger C, Lanzenberger R, Holik A, Spindelegger C, Stein P, Moser U, et al. Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmaco-fMRI: a randomized cross-over study. Neuroimage. 2010;49(2):1161-70.
- Anderson IM, McKie S, Elliott R, Williams SR, Deakin JF. Assessing human 5-HT function in vivo with pharmacoMRI. Neuropharmacology. 2008;55(6):1029-37.
- Arce E, Simmons AN, Lovero KL, Stein MB, Paulus MP. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. Psychopharmacology (Berl). 2008;196(4):661-72.
- Sánchez C, Bøgesø KP, Ebert B, Reines EH, Braestrup C. Escitalopram versus citalopram: the surprising role of the R-enantiomer. Psychopharmacology (Berl). 2004;174(2):163-76.

## DOES PRIOR ANTIDEPRESSANT TREATMENT OF MAJOR DEPRESSION IMPACT BRAIN FUNCTION DURING CURRENT TREATMENT?

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UCLA Department of Psychiatry, Los Angeles, CA

The relationship between prior antidepressant treatment and prefrontal brain functional response to subsequent treatment with antidepressant medication or placebo is unknown. Eighty-nine adults with Major Depressive Disorder (MDD), characterized as antidepressant-experienced or antidepressant-naïve, received one week of single-blind placebo treatment prior to eight weeks of randomized treatment with medication (fluoxetine or venlafaxine; n = 47) or placebo (n = 42) in one of three similar placebo-controlled trials. Brain function was assessed at baseline, end of placebo lead-in, and during randomized treatment using quantitative electroencephalography (qEEG). The authors assessed change in prefrontal theta-band cordance (PFC) in antidepressant-experienced vs. antidepressant-naïve subjects. Treatment history groups differed significantly on PFC change during the placebo lead-in even when controlling for clinical and demographic variables ($F(1,62) = 4.27$, $p = .04$). As assessed in linear mixed models that examined treatment history (antidepressant-experienced or antidepressant-naïve), treatment assignment (medication or placebo), and their interaction as predictors, treatment history also predicted PFC change during the randomized phase of treatment even when controlling for pretreatment clinical and demographic and symptom improvement during treatment ($F(1,5o) = 5.20$, $p = .03$). The interaction was not significant. Post hoc analyses showed that antidepressant-experienced subjects treated with placebo showed PFC changes that did not differ from PFC changes seen in the medication group. Results suggest that prefrontal brain functional changes during treatment for MDD may differ depending upon prior treatment with antidepressant medication.

**Learning Objectives:**

- To gain awareness of the potential impact of one's antidepressant treatment history on brain functional changes observed during subsequent treatment with antidepressant medication or placebo
- To appreciate the research implications of evaluating medication effects on brain activity in subjects with versus without a history of prior treatment

**Source Of Funding:** This work was supported by grants R01 AT003479 and R01 MH069217 from the National Institute of Mental Health, and by grants from Eli Lilly and Company, Wyeth-Ayerst Laboratories, and Aspect Medical Systems.

**Literature References:**

- Amsterdam JD; Williams D; Michelson D; Adler LA; Dunner DL; Nierenberg AA; Reimherr FW, Schatzberg AF: Tachyphylaxis after repeated antidepressant drug exposure in patients with recurrent major depressive disorder. Neuropsychobiology 2009; 59:227-233.
- Benedetti F; Carlino E; Pollo A: How placebos change the patient's brain. Neuropsychopharmacology 2011; 36:339-54.
- Flaten MA; Simonsen T; Waterloo K; Olsen H: Pharmacological classical conditioning in humans. Human Psychopharmacology 1997; 12:369-377.
- Hunter AM; Leuchter AF; Morgan ML; Cook I.A: Changes in brain function (QEEG cordance) during placebo lead-in and treatment outcomes in clinical trials for major depression. Am. J. Psychiatry 2006; 163:1426-32.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## CLINICAL PROFILES OF RESPONSE AND REMISSION IN STAR*D

Felipe A. Jain, MD[1], Aimee M. Hunter, PhD[2], John O. Brooks, MD, PhD[1], Andrew F. Leuchter, MD[1]

[1]UCLA Semel Institute for Neuroscience and Resnick Neuropsychiatric Hospital, Los Angeles, CA, [2]UCLA Semel Institute for Neuroscience, Los Angeles, CA

**Objective:** Several predictors of treatment response have been identified in large cohorts of patients with Major Depressive Disorder (MDD); however, their prognostic utility for individual patients has not been systematically evaluated. We examined the predictive power of baseline clinical and demographic factors, both separately and through use of hierarchical predictive profiles of response and remission during treatment with citalopram.

**Method:** We applied a signal-detection analysis to data from the STAR*D trial to identify the strongest demographic and clinical predictors of treatment outcome. An objective algorithm determined the best cutpoint for each predictive variable by determining its kappa coefficient (a measure of how well the predictor identified the treatment outcome). Applied recursively, the algorithm created hierarchies of predictors.

**Results:** The best individual predictor variables for treatment outcome were years of education, income, employment, private insurance, depression subtypes, severity of depression, distress or arousal from trauma, aches and pains. All variables had low predictive power, but hierarchical combinations improved the ability to predict treatment outcomes. In contrast to an overall 47% response rate in the STAR*D population, profiled patient subgroups were at as low as 31% and as high as 63% rate of response. Contrasting with the 28% remission rate overall, identified subsets of patients had 12% to 55% probability of remission.

**Conclusions:** Although individual baseline socioeconomic and clinical factors have poor predictive power, hierarchical profiles of these variables may identify patients who are at low and high likelihood of benefiting from a single antidepressant trial.

**Learning Objectives:**

- Understand that individual variables have poor predictive power for antidepressant treatment outcome
- Understand that hierarchical variables may improve the predictive power for antidepressant treatment outcome

**Source Of Funding:** None

**Literature References:**

- Trivedi M, et al. Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. American Journal of Psychiatry 2006; 163: 13.
- Kiernan M, et al. Do logistic regression and signal detection identify different subgroups at risk? Implications for the design of tailored interventions. Psychological Methods 2001; 6; 13.

## THE CLINICAL RELEVANCE OF RESULTS ACHIEVED WITH VILAZODONE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

John Edwards, MD[1], Arif Khan, MD[2], Wenjie Song, PhD[1], Adam Ruth, PhD[3]

[1]Forest Research Institute, Jersey City, NJ, [2]Duke University School of Medicine / Northwest Clinical Research Center, Bellevue, WA, [3]Prescott Medical Communications Group, Chicago, IL

**Objective:** Vilazodone, a serotonin reuptake inhibitor and 5-$HT_{1A}$ receptor partial agonist, is approved by the US Food and Drug Administration for the treatment of major depressive disorder (MDD) in adults. Efficacy and safety were established in two 8-week clinical trials (RCT-1: NCT00285376; RCT-2: NCT00683592). To evaluate the clinical relevance of vilazodone, efficacy and safety outcomes from these trials were used to estimate the number needed to treat (NNT) for response and remission, and the number needed to harm (NNH) for adverse events (AEs) and discontinuation.

**Methods:** Post hoc analyses of pooled data from two 8-week, double-blind, randomized, controlled trials (RCT-1 and RCT-2) of vilazodone (n=436) versus placebo (n=433) were conducted. Patients were 18-70 years of age with DSM-IV-TR–defined MDD and a minimum score ≥22 on the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$). Study design was similar in both trials; patients randomized to vilazodone were titrated to a 40-mg target dose, taken once daily with food, over 2 weeks. Mean change from baseline to Week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) and safety variables were assessed in both studies; secondary efficacy endpoints included $HAMD_{17}$, Clinical Impressions-Improvement (CGI-I) and -Severity (CGI-S). Post hoc analyses estimated the effect of vilazodone relative to placebo on NNT for response (MADRS ≥50% improvement, CGI-I ≤2) and remission (MADRS ≤10, MADRS ≤12); NNH for time to discontinuation due to AEs and common AEs were also estimated. For efficacy endpoints, the last observation carried forward (LOCF) approach was used.

**Results:** Pooled baseline demographic and disease characteristics were similar between groups. Pooled MADRS change from baseline was significantly superior for vilazodone versus placebo (LSMD [95% CI] -2.79 [-4.14, -1.44]; $P$<.0001); significant improvement on secondary measures in favor of vilazodone was also seen ($P$<.01 for all 3). The NNT (95% CI) for response was 8 (5, 17) for MADRS ≥50% improvement and 7 (5, 14) for CGI-I ≤2. The NNT (95% CI) for remission was 12 (7, 37) for MADRS ≤10 and 8 (5, 15) for MADRS ≤12. AEs tended to occur early in the course of treatment; 7% of vilazodone- and 3% of placebo-treated patients discontinued due to AEs. The NNH (95% CI) for discontinuation due to AEs was 26 (15, 106).

**Conclusion:** Vilazodone treatment compared with placebo was associated with significant improvement in symptoms of MDD. An NNT for response ≤10 is generally regarded as evidence for clinical relevance in depression treatment. This NNT and NNH analysis suggested a lower risk of discontinuation due to AEs relative to clinically meaningful improvement for vilazodone.

**Learning Objectives:**

- At the conclusion of this session, participants should be able to discuss the clinical relevance of symptom improvement in patients with MDD taking vilazodone.
- At the conclusion of this session, participants should be able to evaluate the clinical risks and benefits of vilazodone in the treatment of MDD.

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

**Literature References:**

- Khan A: 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: 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.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## ADJUNCTIVE ARIPIPRAZOLE DOUBLES THE RATE OF EARLY AND SUSTAINED RESPONSE IN MDD PATIENTS WITH AN INADEQUATE RESPONSE TO ANTIDEPRESSANT MONOTHERAPY

Daniel E. Casey, MD[1], Kimberly K. Laubmeier, PhD[2], James M. Eudicone, MS[2], Ronald Marcus, MD[3], Robert Berman, MD[3], Ross A. Baker, PhD[4], Jack Sheehan, PhD[2]

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**Objective:** The goal of treating major depressive disorder (MDD) is sustained remission of symptoms, [1] ideally beginning early in the course of therapy. However, antidepressant therapy (ADT) often requires 6–8 weeks to determine if it has reached its intended effect, and this delay may impede the successful clinical use of ADT. This post-hoc analysis investigated if the effect of adjunctive aripiprazole on early and sustained response (ESusR) compared with ADT alone. ESusR is a particularly rigorous efficacy measure because patients must respond early (at Week 2) and at all subsequent time points.

**Methods:** Data from three similar studies were pooled. [1,2] All patients had to have an inadequate response to 1–3 trials of ADT. Each study included an 8-week prospective ADT phase (Phase B), followed by a 6-week randomized phase of adjunctive aripiprazole versus adjunctive placebo (Phase C). ESusR was defined as a patient who had a response (≥50% improvement in Montgomery Asberg Depression Rating Scale [MADRS] total score during Phase C) to treatment at Week 2 and sustained that response at all subsequent visits (Weeks 3, 4, 5, and 6) among patients who attended all visits.

**Results:** The rate of ESusR in the adjunctive aripiprazole group was 11.6% (45/387) versus 5.4% (21/387) in the adjunctive placebo group (P=0.002; odds ratio [OR]=2.3, 95% CI: 1.3, 3.9). Out of the overall population, 22.7% (88/387) of adjunctive-aripiprazole treated patients and 10.9% (42/387) of adjunctive-placebo recipients responded at Week 2. Of those who had an early response, 51.1% (45/88) of patients in the adjunctive aripiprazole group and 50.0% (21/42) of patients in the adjunctive placebo group attained ESusR (P=0.904). Among patients who achieved ESusR on adjunctive aripiprazole, the most common adverse events were akathisia (20.0%), restlessness (17.8%), fatigue (13.3%), insomnia (13.3%), and blurred vision (11.1%), which are similar to the general aripiprazole population. [1,2] The mean weekly ending dose of aripiprazole in those who achieved ESusR was 8.5 mg/day, compared with 11.8 mg with adjunctive placebo.

**Conclusions:** Adjunctive aripiprazole treatment produced ESusR more than twice as often as ADT monotherapy. The early onset of adjunctive aripiprazole efficacy may be clinically valuable as it allows for earlier identification of response leading to better patient management.

**Learning Objectives:**

- Demonstrate the efficacy of adjunctive aripiprazole in inducing early and sustained response using a measure of symptoms in patients with major depressive disorder
- Assist clinicians in making earlier treatment decisions for their patients

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

**Literature References:**

- Thase ME, et al. J Clin Psychiatry. 2008;10:440-7.
- Berman RM, et al. CNS Spectr. 2009; 14:197-206.

## DEVELOPMENT OF A NEW DEPRESSION RATING SCALE, THE ROSENBERG MOOD SCALE

Leon I. Rosenberg, MD[1], Howard Hassman[2]

[1]Center for Emotional Fitness, Cherry Hill, NJ, [2]CRI Worldwide, Mt. Laurel, NJ

Documented evidence of patient input and input from experts during the development of a new depression rating scale, the Rosenberg Mood Scale (RMS), is presented. According to the 2009 FDA Guidance for Industry regarding Patient Rated Observations (PROs) "sponsors should provide documented evidence of patient input during instrument development.[1]"

Previous work by the primary author on a PRO depression rating scale, the MRRS-D-SR-FC, includes two posters presented at NCDEU in 2005 and 2008. 10 interviews were conducted in 2011 with experts such as David Sheehan and Stuart Montgomery to assess opinions about the MRRS-D-SR-FC. Input from these 10 experts will be presented. As a result of their input the previous self-rated scale has been replaced with this new PRO, the Rosenberg Depression Rating Scale. (The FDA Guidance document noted "It is expected that the instrument will change as data is collected.[1]")

3 of the 14 characteristics of PRO instruments suggested to be reviewed by the FDA Guidance include the following: concepts being measured; response options; and recall period. This work includes early data on these characteristics.

The primary author established a conceptual framework that severity is equal to frequency. This is in concert with DSM-IV diagnostic criteria for symptoms of MDD; MDD criteria are based upon symptom frequency (i.e., Symptom present most of the day, nearly every day[2]). Frequency of symptoms is the sole measure of severity in this PRO, the RMS, therefore item response options needed to be developed to capture frequency of symptoms.

We chose to use a 7 point Likert Scale with interval constancy and tested it in a diverse patient and a diverse clinician group in response to the FDA Guidance for Industry regarding PROs in this preliminary study of item response options in the RMS in comparison with other existing scales. Complete statistical analysis is in progress.

**Learning Objectives:**

- Understanding PRO development
- Understanding about confounded measures
- Understanding about confounded anchors
- Understanding the specifics of the development of the Rosenberg Mood Scale

**Source Of Funding:** Self-funded

**Literature References:**

- Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Office of Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Room 2201, Silver Spring, MD 20993-0002.
- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association, 2000.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## REPEATED ADMINISTRATIONS OF KETAMINE IN TREATMENT-RESISTANT MAJOR DEPRESSION: RAPID ANTIDEPRESSANT EFFECTS AND DURABILITY OF RESPONSE

James W. Murrough, MD, Andrew M. Perez, MD, Sarah Pillemer, MD, Jessica Stern, MD, Kyle Lapidus, MD, Laili Soleimani, MD, Diogo K. Alves, BS, Dennis S. Charney, MD, Dan V. Iosifescu, MD

Mount Sinai School of Medicine, New York, NY

**Background:** Multiple research reports have found that ketamine is associated with rapid antidepressant effects, even in individuals suffering from treatment-resistant depression (TRD). However, most studies have tested single-dose ketamine administration and measured treatment effects over hours or up to a week. There is limited understanding of the safety and efficacy of ketamine beyond a single administration. In the current study we examined the short and longer-term response to repeated administrations of ketamine over two weeks in TRD.

**Methods:** Participants with TRD (n=23) underwent a washout of antidepressant medication prior to starting a series of six intravenous (IV) infusions of low-dose ketamine (0.5 mg/kg) as monotherapy (administered three times weekly for two weeks). Participants were monitored afterwards for up to 3 months or until relapse.

**Results:** The overall mean change in Montgomery–Asberg Depression Rating Scale (MADRS) score from baseline to treatment endpoint (post infusion no. 6) was 22.8 (mean baseline MADRS score: 32.1±6.0; endpoint MARDS score: 9.3±11.3). 16/23 participants (70%) met response criteria (defined as a ≥ 50% reduction in MADRS score compared to baseline) at endpoint; responder status at endpoint was strongly predicted by response following the first ketamine administration. During the follow up phase, median time-to-relapse was 20 days (range: 4 days to > 3 months).

**Conclusions:** Although limited by small sample size and open treatment design, these data suggest that a series of six IV ketamine infusions may be safe and efficacious in patients with TRD and can produce a durable response in a subgroup of patients.

**Learning Objectives:**

- To understand limitations in the current treatment of major depression
- To understand the experimental evidence for ketamine as a novel antidepressant

**Source Of Funding:** UL1RR029887

**Literature References:**

- Aan het Rot M et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010;67(2):139-45.
- Murrough JW et al. A case of sustained remission following an acute course of ketamine in treatment-resistant depression. J Clin Psychiatry. 2011;72(3):414-5.

## SELEGILINE TRANSDERMAL SYSTEM (STS) FOR MAJOR DEPRESSIVE DISORDER (MDD) WITH ATYPICAL FEATURES: A POST-HOC ANALYSIS OF DATA FROM AN OPEN-LABEL, 10-WEEK TRIAL

Saeheon Jang, MD[1], Sungwon Jung, MD, PhD[1], Chiun Pae, MD, PhD[1], Kimberly Blanchard Portland, PhD[2], Rob Mariani[2], Terry Painter[2], Paul Mastoridis[2], Ashwin A Patkar, MD[1]

[1]Duke University, Durham, NC, [2]Dey Pharma, LP, Basking Ridge, NJ

**Objective:** Approximately 36% of patients with major depressive disorder (MDD) may have atypical features, which may be associated with poorer long-term prognosis. Monoamine oxidase inhibitors (MAOIs) have been shown to be efficacious in treating MDD with atypical features. Selegiline transdermal system (STS) is a novel MAOI that bypasses the gastrointestinal system, thereby reducing the risk for dietary interactions. We investigated the efficacy of STS in MDD patients with atypical features.

**Method:** Data were analyzed from a 10 week, open-label treatment phase of STS 6 mg/24 hrs in patients with MDD. This was the stabilization phase of a 52-week, placebo-controlled double-blind relapse prevention trial with STS. Atypical subtype was defined as at least one score of 2 for items 22¨C26 on the 28-item Hamilton Depression Rating Scale (HAM-D 28). Response was defined as ¡Ý 50% reduction in the HAM-D 17 score and remission as a HAM-D 17 score of <10 at 10 weeks. We used repeated measures ANOVA and t-tests to compare between group differences.

**Results:** 675 patients entered the open-label phase trial. 371 (55%) of patients met criteria for having ¡®atypical features¡¯. In the total sample there was a significant reduction in HAM-D 28 scores from baseline to end of treatment (mean change= - 13.7, CI = -13.0 to -14.3, $p < 0.001$). There were no significant differences in mean HAM-D 28 change from baseline to end of treatment in atypical (mean change = - 13.80, SD = 7.3) versus nonatypical subgroups (mean change = - 13.54, SD = 7.6) ($p = 0.69$). Response and remission rates were 62.5% and 46.5% respectively in the atypical group and 61.8% and 48.0% respectively in the nonatypical group.

**Conclusion:** In this post hoc analysis, STS appeared to be equally efficacious in atypical and nonatypical subtypes of MDD. Further analysis of data from controlled trials is needed to confirm the findings

Key words: Selegiline transdermal system (STS), major depressive disorder, atypical depression

**Learning Objectives:**

- To understand the efficacy of selegiline transdermal system (STS) for MDD patients with atypical features
- To understand the safety and tolerability of STS in an MDD population

**Source Of Funding:** Dey Pharma, LP

**Literature References:**

- Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. J Clin Psychopharmacol. 2006 Dec;26(6):579-86.
- Patkar AA, Pae CU, Masand PS. Transdermal selegiline: the new generation of monoamine oxidase inhibitors. CNS Spectr. 2006 May;11(5):363-75.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## L-METHYLFOLATE PRODUCES A ROBUST EFFECT ON CORE SYMPOMS USING MAIER SUBSCALE SCORES IN A RANDOMIZED CLINICAL TRIAL OF PATIENTS WITH MAJOR DEPRESSION

George I. Papakostas, MD[1], Stephen M. Stahl, MD, PhD[2]

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**Purpose**: Major depressive disorder (MDD) includes a metabolic component that is associated with poor antidepressant response. Addressing the underlying metabolic problem corrects metabolic defects and results in improvements in core symptoms. Both body mass index (BMI) and inflammatory markers including C-reactive protein (CRP) have been shown to be independently associated with MDD (Howren et al, 2009). Increased body weight is associated with decreased response to antidepressants and a greater risk of MDD (Kloiber et al, 2007).

**Objective**: This analysis from a clinical trial of patients with MDD assessed the effect of L-methylfolate 15 mg as an adjunct to SSRIs on the Maier subscale of the HDRS and correlations with an inflammatory biomarker.

**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 sub-analysis of the primary study, mean change from baseline to endpoint was evaluated for the Maier subscale (HDRS items 1, 2, 7-10, and 13) for L-methylfolate and placebo. In addition, correlations between BMI and hs-CRP were examined.

**Results**: 74 patients were included in phase 1 and 39 in phase 2 of the analysis. For pooled data, mean change on the Maier subscale was -3.3 ± 3.7 for L-methylfolate vs. -1.5 ± 3.2 for placebo (95% CI: -2.936, -0.296, p=0.016). Mean improvement in symptoms was significantly greater with L-methylfolate vs. placebo (-7.4 ± 7.9 vs. -2.4 ± 5.3) among patients with a BMI ≥30 kg/m$^2$ (95% CI: -4.410, -0.864, p=0.001). Mean symptom improvement was significantly greater with L-methylfolate than placebo (-7.7 ± 7.4 vs. -3.7 ± 7.5) in patients with elevated baseline hsCRP >median (2.25 mg/L) (95% CI: -7.227, -0.002, p=0.050).

**Importance**: A robust response in core symptoms of MDD on the Maier subscale was observed with L-methylfolate as an adjunct to SSRI treatment. Addressing the metabolic imbalances associated with elevated BMI or inflammation may aid in the robust treatment effect associated with the core symptoms of MDD.

**Learning Objectives:**

- Identify effect of treatment in core symptoms of depression, and in patients with elevated baseline BMI and CRP.
- Recognize that addressing underlying metabolic dysfunction may result in improvement of core symptoms of depression.

**Literature References:**

- Kloiber S, Ising M, Reppermund S, et al. Overweight and obesity affect treatment response in major depression. Biol Psychiatry. 2007;62:321-6.
- Howren MB, Lamkin DM, Suls S. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71:171-86.

## PREDICTORS OF RELAPSE IN A FIXED-DOSE, RANDOMIZED, DOUBLE-BLIND, 52-WEEK RELAPSE PREVENTION TRIAL OF SELEGILINE TRANSDERMAL SYSTEM (STS)

Saeheon Jang, MD[1], Sungwon Jung, MD, PhD[1], Chiun Pae, MD, PhD[1], Kimberly Blanchard Portland, PhD[2], Paul Mastoridis[2], Ashwin A. Patkar, MD[1]

[1]Duke University, Durham, NC, [2]Dey Pharma, LP, Basking Ridge, NJ

**Objective:** The variability in treatment relapse in major depressive disorder (MDD) has led to investigations of the relevance of patient characteristics. We investigated clinical characteristics predictive of relapse in a 52-week controlled trial of selegiline transdermal system (STS).

**Method:** After 10 weeks of open-label stabilization with STS, 322 remitted patients with MDD were randomized to 52-weeks of double-blind treatment with STS (6mg/24hrs) or placebo. Relapse was defined as Hamilton Depression Rating Scale (HAMD-17) score of ¡Ý14 and a CGI-S score of ¡Ý3 with at least 2-point increase from the beginning of double blind phase on 2 consecutive visits. Pretreatment demographics, illness course, treatment resistance and symptom domains were studied to identify predictors of relapse.

**Results:** Significantly fewer STS patients (16.8%) relapsed compared to placebo (30.7%) (p <0.005) and had a significantly longer time to relapse than did placebo (p<0.005). Baseline total HAMD-28 score, somatic anxiety, recurrent MDD, atypical depression, and analgesic use (celecoxib, naproxen) predicted relapse. Significant predictors of differential outcome were identified: 1) high baseline HAMD-28 score (p<0.001), high somatic anxiety ( p<0.05) and celecoxib use (p<0.05) predicted relapse with STS; 2) atypical symptoms (p<0.05), recurrent episodes (p<0.05) and naproxen use (p<0.01) predicted relapse with placebo.

**Conclusions:** For patients on STS, higher baseline depression severity, somatic anxiety or receiving celecoxib predicted relapse, while predictors of relapse with placebo were atypical or recurrent depression or naproxen use. The results provide indirect evidence of treatment specificity by identifying characteristics which may be of value in selection of patients for STS treatment.

Key words: Selegiline transdermal system (STS), major depressive disorder, predictors, relapse

**Learning Objectives:**

- To understand clinical characteristics that may predict relapse with long term treatment with selegiline transdermal system (STS) in patients with major depressive disorder
- To understand the safety profile of STS in a long-term RCT

**Source Of Funding:** Dey Pharma, LP

**Literature References:**

- Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. J Clin Psychopharmacol. 2006 Dec;26(6):579-86.
- Patkar AA, Pae CU, Masand PS. Transdermal selegiline: the new generation of monoamine oxidase inhibitors. CNS Spectr. 2006 May;11(5):363-75.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## POOLED ANALYSIS OF THREE TRIALS OF ADJUNCTIVE ARIPIPRAZOLE IN MAJOR DEPRESSIVE DISORDER PATIENTS: WHAT CGI-S SCORE IS A LOGICAL DEFINITION OF RESPONSE IN DEPRESSION?

Daniel E. Casey, MD[1], Kimberly K. Laubmeier, PhD[2], James E. Eudicone, MS[2], Ronald Marcus, MD[3], Robert Berman, MD[3], Ross A. Baker, PhD[4], Jack Sheehan, PhD[2]

[1]Oregon Health and Science University, Portland, OR, [2]Bristol-Myers Squibb, Plainsboro, NJ, [3]Bristol-Myers Squibb, Wallingford, CT, [4]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ

**Objective:** Criteria for response vary in clinical trials of depression, making comparisons across studies difficult. A ≥50% improvement in Montgomery Asberg Depression Rating Scale (MADRS) Total score is the gold standard definition of response but its relationship to overall clinical progress is unclear. This post-hoc analysis investigated the distribution of Clinical Global Impression-Severity (CGI-S) scores (a measure of clinical state compared with other patients with depression) in relation to MADRS response using pooled data from three similar studies of adjunctive aripiprazole for the treatment of major depressive disorder.[1,2] Week 2 data were analyzed because rapid onset of efficacy helps clinicians make treatment decisions earlier in the course of therapy, potentially improving patient outcomes.

**Methods:** Patients had to have an inadequate response to 1–3 trials of antidepressant therapy (ADT).[1,2] Each study had an 8-week prospective ADT phase (Phase B), then a 6-week randomized phase of adjunctive aripiprazole vs. adjunctive placebo (Phase C). Response (≥50% improvement in MADRS Total score) and CGI-S score was assessed at Week 2 during Phase C.

**Results:** The median and mode CGI-S score at Week 2 among Week 2 MADRS responders was 2 (borderline mentally ill) for both adjunctive aripiprazole (n=88) and adjunctive placebo (n=42). The median and mode CGI-S scores were 4 (moderately ill) among Week 2 adjunctive aripiprazole non-responders (n=299) and adjunctive placebo non-responders (n=345). The distribution of CGI-S scores differed among Week 2 MADRS response and treatment groups ($p<0.0001$), possibly because more responders receiving adjunctive aripiprazole achieved a CGI-S score of 1 (normal, not at all ill) compared with placebo (21.6% vs. 7.1% of responders), and fewer responders receiving aripiprazole achieved a CGI-S score of 3 (mildly ill) compared with placebo (29.6% vs. 40.5% of responders).

**Conclusions:** These results suggest that a CGI-S cut-off score of 2 provides a response threshold most similar to a ≥50% improvement on the MADRS. The differences in CGI-S scores between adjunctive aripiprazole and adjunctive placebo responders are driven by the greater percentage of aripiprazole-treated patients achieving a CGI-S rating of 'not at all ill' after just 2 weeks. This suggests that Week 2 responders receiving aripiprazole may attain a greater overall clinical improvement than placebo responders.

**Learning Objectives:**

- Demonstrate the efficacy of adjunctive aripiprazole in inducing early and sustained responses in patients with major depressive disorder
- Assist clinicians in making earlier treatment decisions for their patients

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

**Literature References:**

- Thase ME, et al. Prim Care Companion J Clin Psychiatry. 2008;10:440-447.
- Berman RM, et al. CNS Spectr. 2009; 14:197-206.

## VILAZODONE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: EFFECTS ON WEIGHT AND LABORATORY VALUES

Michael E. Thase, MD[1], Wenjie Song, PhD[2], John Edwards, MD[2], Adam Ruth, PhD[3]

[1]University of Pennsylvania School of Medicine, Philadelphia, PA, [2]Forest Research Institute, Jersey City, NJ, [3]Prescott Medical Communications Group, Chicago, IL

**Objective:** Vilazodone, a serotonin reuptake inhibitor and 5-$HT_{1A}$ receptor partial agonist, is approved by the US Food and Drug Administration for the treatment of MDD in adults. Efficacy and safety were established in two 8-week clinical trials (RCT-1: NCT00285376; RCT-2: NCT00683592); safety was supported by results from a 52-week open-label trial (OL: NCT00644358). The effects of vilazodone on body weight, body mass index (BMI), and laboratory values were evaluated in post hoc analyses.

**Methods:** Post hoc analyses were conducted on pooled safety data from two 8-week, double-blind, randomized, controlled trials (RCT-1 and RCT-2) of vilazodone (n=436) versus placebo (n=433); additional analyses were performed on 52-week, OL data (N=599). Patients were 18-70 years of age with DSM-IV-TR-defined MDD and a minimum score ≥22 (RCT-1 and -2) or ≥18 (OL) on the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$). Study designs were similar in the 8-week trials; patients randomized to vilazodone or receiving OL treatment were titrated to a 40-mg target dose, taken once daily with food, over 2 weeks. Post hoc analyses of double-blind and open-label data evaluated body weight changes stratified by baseline BMI ($kg/m^2$) categories (underweight, <18.5; normal, 18.5≤ to <25.0; overweight, 25.0≤ to <30.0; obese, ≥30.0). Potentially clinically significant (PCS) weight gain (>7% increase from baseline) and laboratory values associated with liver enzymes and blood glucose were also investigated.

**Results:** Mean baseline body weight (kg) was 86.0 and 86.5 for vilazodone and placebo patients, respectively, in the pooled studies, and 89.6 in the OL study. Mean baseline BMI was 30.2 for vilazodone and 30.1 for placebo patients in the pooled studies (≥70% were overweight or obese) and 31.6 in the OL study. In the pooled studies, mean change in body weight (kg) from baseline to end of treatment (EOT) for vilazodone and placebo patients, respectively, was 0.16 and 0.18 overall, 0.0 and 0.32 for patients with normal BMI, 0.08 and 0.57 for overweight patients, and -0.39 and 0.18 for obese patients. PCS weight gain occurred in 1 vilazodone and 1 placebo patient with normal BMI; in overweight patients, PCS weight gain occurred in 1 vilazodone and 1 placebo patient. In the OL study, mean change in body weight (kg) from baseline to EOT was 1.20 overall, and 1.13, 1.21, 1.50, and 1.06 for underweight, normal, overweight, and obese patients, respectively; PCS weight gain occurred in 2%, 3%, and 5% of normal, overweight, and obese patients, respectively. In the pooled 8-week studies, changes in liver enzymes and blood glucose were small and similar between vilazodone and placebo.

**Conclusions:** In acute and long-term treatment, change in body weight suggested a weight neutral profile for vilazodone across BMI categories; changes in clinical laboratory measures for vilazodone were small and similar to placebo.

**Learning Objectives:**

- At the conclusion of this session, participants should be able to discuss changes in weight and BMI associated with vilazodone in patients with baseline BMI levels categorized from normal to obese.
- At the conclusion of this session, participants should be able to evaluate the effects of vilazodone on clinical laboratory values and parameters.

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

**Literature References:**

- Khan A: 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: 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.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## INTERACTION OF ANTIDEPRESSANT MEDICATIONS AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS DIFFERENTIALLY AFFECTS OUTCOME OF TREATMENT

Marisa Toups, MD[1], Madhukar H. Trivedi, MD[1], Jennifer Warner-Schmidt, PhD[2], Thomas Carmody, PhD[1], Benji Kurian, MD[1], Maurizio Fava, MD[3]

[1]UT Southwestern, Dallas, TX, [2]Rockefeller University, New York, NY, [3]Massachusettes General Hospital, Boston, MA

**Backgound:** Increasing data has implicated inflammation in at least some instances of Major Depressive Disorder (MDD), raising interest in using anti-inflammatory agents for the treatment of depression. Recently, however, in an analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, use of such medications correlated with worsened, rather than improved, outcome in subjects taking Citalopram, a Selective Serotonin Reuptake Inhibitor (SSRI). Here we explored the use of both prescription and non-prescription Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) (including acetaminophen) in the COmbining Medications to Enhance Depression Outcomes (COMED) sample to determine whether NSAIDs affect antidepressant treatment outcome.

**Methods:** COMED enrolled adults with chronic or recurrent MDD were randomized to one of three treatment arms, each consisting of a primary open label antidepressant, and a secondary, single blinded medication started at week two. The main aim of COMED was to compare remission across one single medication arm (escitalopram + placebo) with two medication combination arms (bupropion + escitalopram and venlafaxine + mirtazapine). NSAID (and NSAID combination drug) use data was extracted from patient reports of all concomitant medications at each study visit. Subjects who reported NSAID use at any post baseline visit over the study period were classified as NSAID users. Unadjusted and adjusted (for age, gender, depression severity and number of medical problems) generalized linear mixed models were run to assess the effect of NSAIDs on outcome.

**Results:** In the adjusted analysis for treatment arm by NSAID use interaction, a significant differential effect was found (p=0.033). While subjects in the escitalopram plus placebo arm who were also NSAID users had lower remission rates (34.4%) than those who were not taking NSAIDs(45.0%), in the other two arms NSAID use was associated with higher remission rates (42.3% vs. 36.7% for bupropion + escitalopram and 44.9% vs. 29.6% in the venlafaxine + mirtazapine arm).

**Discussion:** These results support the previous finding from the STAR*D sample, namely that NSAID use may have a deleterious effect on the outcome of SSRI treatment. However we found a strong differential effect suggesting that NSAIDs may be beneficial when given with some specific types of antidepressants. More trials examining this result prospectively are needed to verify the effects of NSAIDs on antidepressant responses; in particular, studies directly assessing inflammatory markers during treatment may elucidate the mechanism of the effect.

**Learning Objectives:**

- To explore how anti-inflammatory agents affect treatment of MDD
- To determine if such effects are clinically relevant

**Source Of Funding:** NIMH N01 MH-90003

**Literature References:**

- Rush, J et al. Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study. America Journal of Psychiatry 2011; 168:689-701.
- Warner-Schmidt, JL et al. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflammatory drugs in mice and humans. Proceedings of the National Academy of Sciences 2011;108: 9262-7.

## THE IMPACT(S) OF FAMILY PSYCHIATRIC HISTORY ON SIGNAL DETECTION AND PLACEBO-RESPONSE: META-ANALYSIS

Charles S. Wilcox, PhD[1], Nader Oskooilar, MD, PhD[2], Judy L. Morrissey[3], Daniel E. Grosz, MD[3], Mellissa M. Henry[2], Kimberly Guevarra[1], Don De Francisco, MD, PhD[1]

[1]Pharmacology Research Institute [PRI], Newport Beach, CA, [2]Pharmacology Research Institute [PRI], Los Alamitos, CA, [3]Pharmacology Research Institute [PRI], Encino, CA

**Purpose:** To investigate the recent report(s) of family psychiatric history having a potential impact on both signal detection and placebo response in antidepressant efficacy studies, we performed a meta-analysis encompassing six recently completed placebo-controlled double-blind trials at our research center.

**Content:** We statistically analyzed data involving 217 adult outpatients diagnosed with Major Depressive Disorder (MDD). The study participants were randomly assigned to either (monotherapy) active treatment with an antidepressant or placebo. Our review indicated that 45.6% (n=99) of the patients had a positive family history of depression (either unipolar or bipolar) and 54.4% (n=118) reported no family history of depression.
Methodology: For the primary statistical analyses we categorized patients by (a) their positive or negative family history of depression, (b) treatment group assignment (i.e., active treatment versus placebo) and (c) baseline to endpoint response rate on the primary outcome measure – the Montgomery-Åsberg Depression Rating Scale (MADRS). Patients with a 50% or greater reduction were categorized as responders, while all patients with 49% or less reduction were non-responders.

**Results:** When analyzed by family psychiatric history and treatment group, the lack of impact of family history was remarkable. The drug response was within one percentage point for patients with a positive family history (n=56) versus patients with no reported family history of depression (n=74). The response rate amongst the placebo patients was statistically identical for participants with a family history (n=43) versus patients assigned to placebo (n=44) who reported no family history of depression. Furthermore, the overall pooled results indicated that independent of family history, those assigned to active treatment (n=130) demonstrated drug efficacy on both the MADRS (p=.032) and CGI-S (p=.029), as compared with the pooled placebo patients (n=87), both with and without a family history of depression.

**Conclusions:** Our results strongly indicate that a family history of depression has very little, if any, impact on both signal detection and placebo response in the context of double-blind placebo-controlled antidepressant efficacy studies.
While our findings conflict with the recent report(s), they are consistent with previously published STAR*D results[(1)] as well as published work in the late-1990s[(2)].

**Learning Objectives:**

- To evaluate the potential impact(s) of psychiatric family history in antidepressant trials.
- To analyze the potential impact(s) of psychiatric family history on signal detection.
- To investigate the possible correlation between psychiatric family history and placebo response.

**Source Of Funding:** Funding for the data compilation, review and this meta-analysis was provided (internally) by Pharmacology Research Institute.

**Literature References:**

- Husain MM, Rush AJ, Wisniewski SR, McClintock SM, Fava M, Nierenberg AA, Davis L, Balasubramani GK, Young E, Albala AA, Trivedi MH: Family history of depression and therapeutic outcome: findings from STAR*D. J Clin Psychiatry 2009 Feb;70(2):185-195.
- Klein DN, Shatzberg AF, McCullough JP, Dowling F, Goodman D, Howland RH, Markowitz JC, Smith C, Thase ME, Rush AJ, LaVange L, Harrison WM, Keller MB: Age of onset in chronic major depression, relation to demographic and clinical variables, family history and treatment response. J Affect Disord 1999 Oct;55(2-3):149-157.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## PSYCHOMETRIC EVALUATION OF THE BROWN ASSESSMENT OF BELIEFS SCALE

Katharine A. Phillips, MD[1,2], Ashley S. Hart, PhD[1], William Menard[1], Jane L. Eisen, MD[2]

[1]Rhode Island Hospital, Providence, RI, [2]Warren Alpert Medical School of Brown University, Providence, RI

**Background:** The Brown Assessment of Beliefs Scale (BABS), a 7-item, semi-structured, rater-administered scale, assesses insight/delusionality – an important dimension of psychopathology – both dimensionally and categorically (e.g., delusional vs nondelusional). It is widely used in studies of OCD and body dysmorphic disorder (BDD). The BABS has strong reliability, validity, and sensitivity to change in OCD, BDD, and psychotic depression, and strong reliability and validity in schizophrenia/schizoaffective disorder (1,2). Sample sizes in these studies were relatively small. This report examines the BABS's psychometric properties in a larger sample of BDD subjects.

**Method:** 301 BDD subjects (*n*=191 from a BDD course study and *n*=110 from BDD medication studies) were interviewed with the BABS to assess insight regarding appearance beliefs (e.g., "I look deformed"), BDD-YBOCS (current BDD severity), 17-item HAM-D, and BPRS. BABS psychometric properties were examined.

**Results:** Mean BABS total score reflected poor insight (15.9 $\pm$ 6.0 for the full sample; 16.6 $\pm$ 5.2 for the 282 subjects with current BDD). ICCs demonstrated good interrater reliability across 2 raters (*n*=23) for BABS total score (.99) and individual items (.68 to .99; median=.97, all *p*'s<.001). Cronbach's alpha coefficient was .88, indicating good internal consistency. Correlations between each item and the total score minus that item were *r*=.58 to .84 (median=.69, all *p*'s<.001). The test-retest ICC (*n*=32) over one week was .93 for BABS total score and .63 to .91 (median=.77, all *p*'s<.001) for individual items. Principal components factor analysis using varimax rotation identified 1 factor accounting for 61% of the variance; factor loadings were .51 to .91. BABS total score correlated *r*=.60 (*p*<.001) with BDD-YBOCS total score and *r*=.28 (*p*<.001) with HAM-D total score; however, BDD and depression severity accounted for only 36% and 8% of the variance in BABS score, respectively. BABS total score was not significantly correlated with BPRS total score (*r*=.22, *p*=.08). Among medication study subjects who received active treatment (*n*=77), the mean BABS score significantly decreased from baseline to post-treatment (*t*=8.09, *p*<.001), indicating sensitivity to change.

**Conclusions:** These findings provide further evidence that the BABS is a reliable and valid measure of insight/delusionality in BDD.

**Learning Objectives:**

- To learn about the BABS, a widely used measure of insight/delusionality
- To learn about new data on the BABS's psychometric properties

**Source Of Funding:** National Institute of Mental Health (R01-MH60241; R29-MH54841; 5 K24-MH063975); Forest Laboratories; UCB Pharma

**Literature References:**

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- Kaplan GB, Phillips KA, Vaccaro A, Eisen JL, Posternak MA, MacAskill HS. Assessment of insight into delusional beliefs in schizophrenia using the Brown Assessment of Beliefs Scale (letter). Schizophrenia Res 2006;82:279-281.

## ATTITUDES OF INVESTIGATORS AND SITE STAFF TOWARD PLACEBO RESPONSE IN INTERNATIONAL CNS CLINICAL TRIALS

David G. Daniel, MD[1], Antony Loebel, MD[2], Josephine Cucchiaro, PhD[3], Jean Dries[4]

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**Background:** In CNS clinical trials there is increased concern with signal detection capability in part due to increased placebo response (1). We recently reported the attitudes of 63 US investigators and their staffs with respect to their ability to influence placebo response (2).In the current report we expanded this sample to include additional international trialists.

**Method**: 165 site investigators and staff from the US, central Europe, India and Japan attending regional industry sponsored investigators' meetings for a double blind, placebo controlled, bipolar depression clinical trial, answered questions administered by an audience response system addressing their ability to influence placebo response. Subsequently investigators and staff were trained in placebo response management using interactive slide presentations and case oriented discussion. The associations of responses to role in the study, the number of previous trainings aimed at reducing placebo response and the proportion of time spent in clinical activities or care unrelated to research were evaluated using the chi-square test statistic.

| Question | Markedly | Moderately | Slightly | Not At All |
|---|---|---|---|---|
| "I can influence the magnitude of placebo response in a clinical trial." | 34.4 % (n=52) | 31.8% (n=48) | 17.2% (n=26) | 16.6% (n=25) |
| "The behavior of site staff in a clinical trial can influence the magnitude of placebo response." | 43.4% (n=66) | 37.5% (n=57) | 15.1% (n=23) | 4.0% (n=6) |

| | Disagree | Agree |
|---|---|---|
| "My role in a clinical trial includes ensuring that subjects improve clinically." | 75.5% (n=117) | 24.5% (n=38) |
| "It is unethical to continue subjects in a clinical trial who are not improving." | 62.9% (n=95) | 37.1% ( n=56) |

69.3% (n=109) had previously received training to reduce placebo response. 48.9% (n=65) identified themselves as "Study Coordinators/Raters" and 51.1% (n=68) as "Investigators/Sub-Investigators". Investigators/Sub-investigators were more likely than Study Coordinators/Raters to *disagree* that "My role in a clinical trial includes ensuring that subjects improve clinically."(p<0.05).Increased exposure to placebo response training was associated with 1) increased confidence that the respondent's individual behavior (p<0.01) or the site staff's behavior (p<0.01) can influence the magnitude of placebo response in a clinical trial; 2) and disagreement with the notions that the respondent's role in a clinical trial includes ensuring that patients improve clinically (p=0.001) or that it is unethical to continue subjects in a clinical trial who are not improving (p<0.05). Attitudes toward placebo response did not vary significantly with the proportion of time spent in clinical activities or care unrelated to research.

**Conclusions:** Investigators and site staff in this international cohort reported a high level of agreement on the importance of placebo response and their ability to influence it in clinical trials. Increased exposure to placebo response training was associated with increased confidence in the ability to modulate placebo response and diminished belief that patients should improve during clinical trial participation. Future presentations will address specific regional findings. Further research should investigate which approaches to placebo response minimization are most effective.

**Learning Objectives:**

- Inform audience of attitudes of clinical trialists toward placebo response
- Inform audience of association between exposure to placebo response training and attitudes toward placebo response

**Source Of Funding:** Sunovion Pharmaceuticals, Inc and United BioSource Corporation

**Literature References:**

- Yang et al: Cur Topics in Med Chem 2005:1077-1086.
- Daniel DG, Loebel A, Cuchiarro J, Dries J: Understanding of Influence of Placebo Response by Investigators and Site Staff in CNS Clinical Trials. NCDEU Annual Meeting Poster 2011.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## INFLUENCE OF 3 PROTOCOL-SPECIFIC ELIGIBILITY CRITERIA ON SIGNAL DETECTION

Gary S. Sachs, MD[1], Douglas Vanderburg, MD[2], Suzanne Edman, BS[3]

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**Introduction:** High failure rates of randomized controlled trials (RCT) are well-recognized but poorly understood. We report exploratory analyses from a failed double-blind study of adjunctive ziprasidone for adults with bipolar I, acute mania. Data collected by computer interviews and by site-based raters (SBR) were analyzed to examine the impact of eligibility criteria on signal detection.

**Methods:** Tandem clinical assessments including SBR and computer-administered versions of the Young Mania Rating Scale were used to categorize subjects as eligible or ineligible on 3 key protocol specified eligibility criteria. Exploratory statistical analyses compared treatment efficacy for eligible versus ineligible subgroups and the impact of rating quality. Criteria were considered "impactful" if the difference between eligible and ineligible subjects on the YMRS change scores was ≥ 1 point.

**Results:** Of 504 subjects with baseline and ≥ 1 post-randomization computer-administered assessments only 180 (35.7%) met all 3 eligibility criteria. There were no statistically significant differences between treatment groups in change from baseline YMRS based on SBR or computer assessments. All criteria tested improved signal detection except excluding subjects with ≥25% improvement from screen to baseline. The most robust criterion was meeting DSM IV criteria for Mania. The difference in drug-placebo separation for subjects eligible vs ineligible by this criterion was 2.7 points based on the SBR scores and 3.3 points based on the computer scores.

**Conclusions:** Based on computer assessments, nearly 2/3 of subjects randomized were ineligible. The trend for better signal detection among subjects meeting computer-assessed eligibility was most robust for eligible subjects with more reliable ratings. Enrollment of ineligible subjects is likely to contribute to failure of acute efficacy studies.

**Learning Objectives:**

- Understand the influence of common entry criteria on signal detection
- Evaluate causes of clinical trial failure.

**Source Of Funding:** Bracket Internal Funds

**Literature References:**

- Greist JH, Mundt JC, Kobak K. Factors contributing to failed trials of new agents: can technology prevent some problems? J Clin Psychiatry. 2002;63(suppl 2):8–13.
- Reilly-Harrington NA, Debonis D, Leon AC, et al. The interactive computer interview for mania. Bipolar Disord. 2010;12(5):521–527.

## SCIENTIFIC AND ECONOMIC BENEFITS OF SEQUENTIAL PARALLEL COMPARATIVE DESIGN (SPCD), A COST EFFICIENT APPROACH TO THE PROBLEM OF PLACEBO RESPONSE

Matt Bowman[1], Ilan M. Fogel, MD[2], Michael B. Knable[3]

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**Introduction:** Placebo response has become an increasingly significant challenge, one which in the best case scenario forces the use of a larger 'n', thus increasing cost and lengthening time to market, or in the worst case scenario leads to failure of a trial and potential termination of product development. In order for a New Drug Application to be approved by the FDA, study drug must be proven superior to placebo in at least 2 pivotal trials. It is estimated that the placebo response rate in trials for Major Depressive Disorder (MDD) is 35-45%. Sequential Parallel Comparative Design (SPCD) is a cost efficient clinical trial method, developed at Massachusetts General Hospital (MGH), that may be able to reduce placebo response rates and the expense of clinical trials.

**Methods:** An SPCD trial involves two phases (i.e. stages) of treatment. Phase 1 is aimed at: (1) comparing drug and placebo, and (2) generating a cohort of placebo non-responders. Phase 2 is aimed at comparing drug and placebo, as in a conventionally designed trial, but utilizing individuals who were placebo non-responders in Phase 1. Sample sizes and power for standard design and for SPCD trials were computed using 1 and 2 degree of freedom score tests and various assumptions regarding differences between drug and placebo response rates (Ivanova, et al. ,2011)

**Results:** When estimating sample size at assumed levels of statistical power, the SPCD method typically allowed for a 20 - 50% reduction of sample size. Likewise, when estimating statistical power with given sample sizes, the SPCD method allowed for a 10-25% increase in statistical power.

**Conclusions:** It is estimated that the SPCD design would be associated with significant savings in direct clinical trial costs, decreased time to market for new drugs, and reduced costs associated with "failed" trials.

**Learning Objectives:**

- To educate the reader as to the need for innovative clinical trial design
- To explain the specific methodology of SPCD together with the associated cost efficiencies

**Source Of Funding:** RCT Logic LLC

**Literature References:**

- Chen Y.et al.: Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials; Contemporary Clinical Trials 32 2011; 592- 604.
- Ivanova A. et al.: Optimality, sample size and power calculations for the sequential parallel comparison design; Statistics in Medicine 2011; 30:2793-2803.
- Fava M. et al.: The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach; Psychotherapy and Psychosomatics 2003; 72:115-127; and "Erratum" 2004; 73: 123.
- Fava M. et al.: A Double-Blind, Placebo-Controlled Study of Aripiprazole Adjunctive to Antidepressant Therapy (ADT) Among Depressed Outpatients with Inadequate Response to Prior ADT (ADAPT-A Study); Psychotherapy and Psychosomatics 2011; Accepted for publication.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## GOING ELECTRONIC: MOVING DATA AND DISCOVERY TO PHARMACOLOGY TEACHERS

Ira Glick, MD

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**Introduction:** Over the last four decades, there has been increasing difficulty in transmitting advances in psychopharmacology to the field. One of the major reasons is that it has been very difficult for teachers to stay up to date and to cover the expanding field. The ASCP has attempted to fill this gap by preparing three Model Curricula—for residents, medical students and most recently family physicians. We now describe the process of making these publications readily available to a world-wide audience by providing the means to purchase and download them via the internet.

**Methodology:** We have in our database over 80 lectures with more than 4,000 slides covering the field of psychopharmacology. Lectures have been collected from expert-academics in a particular field and reviewed by a select committee. Each lecture has a core one-hour set of slides with supplementary slides to be used at the lecturer's discretion. The curriculum has been composed of hard copy plus CDs—we have this year (2011) moved all the content to an electronic format, and have made the content available to purchase and download from the ASCP website.

**Results:** We will present a table of contents for all three curricula. We describe how each will be made available on the web including pricing.

**Summary and Conclusion:** Going electronic has the potential to improve the teaching and learning of psychopharmacology for students, clinicians and others in the field. This new delivery option for the ASCP curriculum makes it easily accessible to anyone, anywhere in the world and lowers the cost of purchase and access. Obstacles to successful implementation will be described.

**Learning Objectives:**

- At the conclusion of the session, the participants who are teachers, will be aware of new psychopharmacology teaching materials for psychiatric residents.
- At the conclusion of the session, the participants who are teachers, will be aware of new psychopharmacology teaching materials for medical students and primary care physicians.

**Source Of Funding:** None

**Literature References:**

- ASCP Model Psychopharmacology Curriculum for Training Directors and Teachers of Psychopharmacology in Psychiatric Residency Programs, 6th Ed.
- ASCP Model Psychopharmacology Curriculum for Directors of Medical Student Education and Teachers of Psychopharmacology in Medical Student Programs.

## PSYCHIATRY ON YOUTUBE: INFORMATION OR MISINFORMATION?

Aashna Mago, Rahul Gupta, Rajnish Mago, MD

Thomas Jefferson University, Philadelphia, PA

**Background:** YouTube is the world's most popular online video community, allowing billions of people to watch and share originally-created videos. However, its content may be harmful or helpful to patients and families.

**Methods:** Searches were conducted on www.YouTube.com using search terms related to psychiatry: "psychiatry," "antidepressants," "antidepressant side effects," "bipolar disorder," "suicide," etc. Data was systematically gathered on content themes, number of views, number of "likes/dislikes," and uploaders. Videos were rated by two independent raters as predominantly negative or positive about psychiatric treatment.

**Results:** Videos were predominantly negative for 60% (psychiatry) to 100% (antidepressants) of the top videos.

Commonest theme for "psychiatry" was that mental disorders are arbitrary. For "antidepressants," commonest themes were that antidepressants don't work and have dangerous side effects. Suicide attempts in the news items was the commonest theme for "suicide." For "How to commit suicide," none of the top videos were either helpful or specifically facilitated suicide. Prank videos from juveniles and videos of attempted suicide were had view counts up to 1,138,790. For "suicide," the National Suicide Prevention Lifeline was "promoted" by YouTube to the top of the list, the only example of helpful promotion in our searches.

Videos were infrequently uploaded by psychiatry professionals/ organizations in 0% (antidepressants) to 30% (psychiatry) cases. More frequently they were uploaded by patients, therapists, non-profits, law firms, etc. Credentials of uploaders were indeterminable for 25% to 44% of videos. Of 10 leading organizations, only APA has a "channel" on YouTube, and only 4 videos have been posted by APA over 2 years. Of 10 leading psychiatry departments, only Yale (one video) and Duke (TV interviews only) have YouTube channels.

Most videos (99.3%) were not rated as either "Likes" or "Dislikes" by viewers. "Likes" exceeded "Dislikes" in all cases.

**Discussion:** YouTube mainly contains videos likely to negatively affect the views of patients and their families about psychiatric treatment. Ratings by viewers are rare and not a protection against misinformation. Majority of the videos are posted by persons whose identity, qualifications, and motivation are questionable or indeterminate.

YouTube should require a statement about the uploader's qualifications and "promote" videos from reputable sources. Psychiatry organizations and departments are urged to develop channels and post scientifically accurate and balanced videos helpful to mental health professionals, patients, families, and the public.

**Learning Objectives:**

- On completion of this activity, attendees will be able to identify 5 leading themes in YouTube videos related to psychiatry
- On completion of this activity, attendees will be able to list 3 problems related to YouTube videos related to psychiatry

**Source Of Funding:** None

**Literature References:**

- Vogel L. Dr. YouTube will see you now. CMAJ. 2011;183(6):647-8.
- Hayanga AJ, Kaiser HE. Medical information on YouTube. JAMA. 2008;299(12):1424-5.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## A STRUCTURED INTERVIEW FOR ASSESSING GLOBAL IMPRESSIONS

David Walling, PhD[1], Celine Houser[2], Joanne Northcutt, PhD[3], Ira Glick, MD[4], Andrew Cutler, MD[5], Donald J. Garcia, MD[6], Michael Downing, MD[7], Jessica A. Little, PhD[2], Steven D. Targum, MD[8]

[1]Collaborartive Neuroscience Network, Garden Grove, CA, [2]Clintara LLC, Canton, MA, [3]Florida Clinical Research Center, LLC, Maitland, FL, [4]Pacific Research Partners, Oakland, CA, [5]Florida Clinical Research Center, LLC, Bradenton, FL, [6]FutureSearch Trials, Austin, TX, [7]FutureSearch Trials, Dallas, TX, [8]Clintara LLC, Canton, MA

**Background:** The Clinical Global Impressions of Severity scale (CGI-S) is widely used in clinical trials. However, both inter-rater reliability and scoring precision are limited because there is no standardized interview procedure to derive the severity scores. We developed a structured interview guide for global impressions (SIGGI) that provides scoring guidelines and specific queries to identify acute symptoms and assess the clinical relevance and impact of these symptoms on behavior and function.

**Method:** 71 subjects from 5 clinical trial sites consented to participate in this study. These subjects were being screened for participation in a clinical trial and had diagnoses of either Major Depressive Disorder (MDD) or schizophrenia. The SIGGI was administered by two independent site-based raters using an audio-digital pen recorder and subsequently by a blinded, site-independent rater. Symptom severity scores were obtained from the MADRS for MDD and the PANSS for subjects with schizophrenia. Correlations were calculated between the SIGGI derived CGI severity score and these symptomatic measures based upon the subject's diagnosis.

**Results:** CGI-S scores ranged from 3 to 6 (mild to marked illness) in this study population. There was a high correlation on the CGI-S scores between the two site-based raters (r= 0.768) and between each site-based rater with the blinded rating (r= 0.705 and 0.867). The SIGGI derived CGI-S scores were correlated with the MADRS (r=0.599) and the PANSS (r= 0.566) scores.

**Conclusions:** A structured interview may improve the precision of scoring for global impressions and therefore enhance the usefulness of the assessments.

**Learning Objectives:**

- The describe a structured interview to standard scoring of global impressions
- To describe reliability testing to confirm utility of this instrument
- To understand the manageable factors that may influence CNS trial success

**Source Of Funding:** Clintara LLC

**Literature References:**

- Guy W: ECDEU Assessment Manual for Psychopharmacology, Revised (DHEW Publication ADM-76-338); 1976: 218-222.
- Targum SD, Busner J, Young AH: Targeted scoring criteria reduces variance in global impressions. Human Psychopharmacol: Clin and Exp., 2008; 23: 628-633.
- Leon AC, Marzak PM. More reliable outcome measures can reduce sample size requirements. Arch Gen Psychiatry. 1995; 52:867–871.

## OLANZAPINE, MELATONIN SUPPRESSION AND WEIGHT GAIN

Nael Kilzieh, MD[1,2], Dennis D. Rasmussen, PhD[2,3], Murray A Raskind, MD[2,3], Annette Kennedy[4], Amanda E. Wood, PhD[1,2], Andre Tapp, MD[1,2]

[1]VAPSHCS, Tacoma, WA, [2]University of Washington, Seattle, WA, [3]VAPSHCS, Seattle, WA, [4]Sheridan VAMC, Sheridan, WY

**Objective:** Animal research suggests olanzapine-induced increases in body weight and visceral adiposity may be, at least in part, secondary to olanzapine-induced reduction of plasma melatonin levels. We conducted a pilot study in psychiatric patients treated with olanzapine to examine 1) if olanzapine is associated with melatonin suppression and 2) if so, what dose of melatonin supplementation reverses this suppression.

**Method:** Ten patients diagnosed with schizophrenia (N=3), schizoaffective bipolar type (N=3), or bipolar disorder (N=4) completed the study. All patients were male, age 50.6±7 years. Patients were treated with olanzapine for 6 weeks, then randomized to one of two groups of melatonin supplementation: 0.3mg (N=4) or 3mg (N=6), in addition to olanzapine, for another 6 weeks. We obtained baseline, week-6, and week-12 measures of the major metabolite of melatonin in the urine, 6-Sulfatoxymelatonin (aMT6s) adjusted for creatinine excretion.

**Result:** Olanzapine treatment was associated with a non-significant decrease in urinary aMT6s (ng/ml) (Mean±SD) from baseline (14.74±10.94) to week-6 (12.32±10.75) (p= .14). Analysis of a sub-sample of patients diagnosed with schizoaffective (bipolar type) or bipolar disorder showed a significant decrease from baseline (16.05±10.21) to week-6 (11.42±9.16) (p=.02). Supplementation with melatonin significantly increased Urinary aMT6s from week-6 (12.32±10.75) to week-12 (1347.8±1000.5) (p=.02). Even patients on 0.3mg dose had an increase to 166.5±149.6.

**Conclusion:** Consistent with animal data, Olanzapine is associated with melatonin suppression in patients reaching significance in those with schizoaffective/bipolar disorder. Low-dose melatonin is adequate to reverse this suppression. Further larger samples are required to confirm this finding and examine its implications on olanzapine-related weight gain.

**Learning Objectives:**

- Participants will learn about metabolic effects of second generation antipsychotic medications
- Participants will learn about new mechanism which may be related to weight gain with such agents

**Source Of Funding:** Eli Lilly. Grant # F1D – MC – X302

**Literature References:**

- Newcomer JW: Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J Clin Psychiatry 2007; 68 Suppl 1:20-7.
- Raskind MA; Burke BL; Crites NJ; Tapp AM; Rasmussen DD: Olanzapine-induced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. Neuropsychopharmacology. 2007; 32(2):284-8.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## THE IMPACT OF PATIENT RECRUITMENT METHODS ON DATA QUALITY

Brian D. Hunter[1], Patricia Brown, PhD[1], Linda Harper, MD[1], John Mark Joyce, MD[2], Susan Angel, MS[2], Leann Carmichael, MS[3], Lora McGill, MD[4]

[1]Clinical Neuroscience Solutions, Inc, Orlando, FL, [2]Clinical Neuroscience Solutions, Inc., Jacksonville, FL, [3]Clinical Neuroscience Solutions, Inc, Memphis, TN, [4]Clinical Neuroscience Solutions, INC, Memphis, TN

Robust enrollment is essential to the successful execution of a clinical trial. This need adds to the growing pressure on sites and sponsors alike brought on by the increasing number of failed trials and increasing rates of placebo response. For the industry to survive, it is imperative that the push for meeting enrollment goals is balanced with the drive for high-quality data. Selecting trial sites that can enroll and retain patients as well as contribute accurate and clean data is a must if the industry is to continue bringing new and improved medications to market.

In response to the increasing pressure to meet enrollment goals, sites need to place considerable emphasis on recruitment. The first step in any site meeting the enrollment goal for a trial is identifying a pool of potential patients that is much larger than the target number to be enrolled. How to recruit depends on the demographics of the target population and the condition under study. Patients from investigators own practices or databases from free standing centers are often the first considered for inclusion into a study. Often these strategies are not enough and the site will need to develop recruitment strategies beyond an existing patient base. This typically includes utilizing direct-to-consumer advertising to attract potential patients that would otherwise be unknown to the site.

While this recruiting practice has become more commonplace, many questions remain regarding the effect such efforts have on the quality of the data collected. This poster examines data collected from three sites to determine whether the manner in which a patient was recruited into a clinical trial affected data quality. Specifically, the rates of screening failure, study completion, early discontinuation, and becoming "lost to follow up" for patients who were recruited through the sites' databases and those that were recruited through advertising were compared. In the interest of simplifying the analysis, only patients enrolled in double-blind trials with an indication of Major Depressive Disorder during 2010 and 2011 were included. The descriptive analysis yielded interesting trends with potentially far-reaching implications for sites throughout the industry.

**Learning Objectives:**

- Compare outcomes for patients recruited through advertising to those recruited through investigators' databases.
- Discuss the need for balance between meeting enrollment goals and maintaining data quality.

**Source Of Funding:** Clinical Neuroscience Solutions, Inc.

**Literature References:**

- Anderson, D. A guide to patient recruitment: Today's best practices and proven strategies. Boston: CenterWatch; 2001.
- Frank, G. Current challenges in clinical trial patient recruitment and enrollment. SoCRA SOURCE. 2004 Feb; 30-38.

## TEST-RETEST RELIABILITY OF FMRI MEASURES OF AMYGDALA ACTIVATION ELICITED BY EMOTIONAL STIMULI AMONG HEALTHY ADULTS

Colin Sauder, MS[1], Joseph C. Blader, PhD[1], Greg Hajcak, PhD[1], Mike Angstadt, BS[2], K. Luan Phan, PhD[3]

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**Overview:** Functional neuroimaging provides information about brain activity that may represent both state and trait features relevant to psychopathology, and is therefore a potentially important tool for evaluating biomarkers of treatment response. The precision and quality of inferences that fMRI offers, however, depend on the reliability of its measurement. Spurious variation over time holds particularly strong relevance for repeated-measures designs that evaluate the effects of medications on potential CNS targets. For example, the amygdala has been linked to emotional processing and regulation as well as behavioral inhibition, and consequently, numerous fMRI studies have focused on this structure. However, inconsistent results from these studies raise the possibility that measurement unreliability introduces noise in these data. Few studies, though, have evaluated the test-retest reliability of fMRI data from this region. Indeed, only one small study to date has assessed the reliability of amygdala response over multiple scanning sessions, and this study employed a form of stimulus presentation that is rarely used in contemporary imaging studies. In the current study we evaluate the test-retest reliability of fMRI data collected using a popular task with demonstrated findings in numerous psychiatric populations.

**Method:** 27 healthy volunteers completed a variation of the face-matching paradigm developed by Hariri et al. (2000) at two time-points 90 days apart. Neural response to faces in contrast to shapes was calculated on both occasions and intra-class correlation coefficients (ICCs) were calculated to assess reliability over time.

**Results:** Consistent with previous studies, emotionally expressive faces (fearful, happy, angry) elicited significantly greater amygdalar activation. However, the temporal stability of the magnitude of subjects' task-related activity within this structure was poor. ICCs for happy and angry faces were not significantly different from zero. The reliability estimates for fearful faces were significant bi-laterally, although only modestly reliable for single assessment (ICC-single = .35) and moderate across time (ICC-average = .50).

**Conclusions:** Findings indicate that the reliability of the BOLD MR signal from a brain structure important to psychiatric illness varies widely by stimulus type and is at best, moderate. Test-retest reliability differed across facial expressions, with the most stable data obtained for fearful expression, but still well below reliability needed for a biomarker either to show sensitivity of drug effects with feasible sample sizes or to serve as a surrogate endpoint. Meanwhile, estimates of single assessment reliability were also low, placing an upper limit on the validity of studies evaluating the relationship between amgydala response and other measures. Compensatory efforts to improve measurement precision, enlarge sample sizes, or increase number of assessment occasions seem warranted.

**Learning Objectives:**

- Reliability of fMRI as a biomarker in treatment studies
- fMRI methods
- Neural correlates of emotion processing

**Source Of Funding:** NIH Grant MH076198 and VA Merit Review Award

**Literature References:**

- Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: effects of a neocortical network on the limbic system. NeuroReport. 2000;11(1):43-8.
- Johnstone T, Somerville LH, Alexander AL, Oakes TR, Davidson RJ, Kalin NH, et al. Stability of amygdala BOLD response to fearful faces over multiple scan sessions. NeuroImage. 2005;25(4):1112-23.
- Wiedemann K. Biomarkers in development of psychotropic drugs. Dialogues Clin Neurosci. 2011;13(2):225-234.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## HEALTH ECONOMIC MODELING SCHIZOPHRENIA OUTCOMES USING TIME TO EVENT SIMULATION

Nicolas M. Furiak, MS, Harry J. Smolen, MS, James C. Gahn, BS, Megha Bansal

Medical Decision Modeling Inc., Indianapolis, IN

**Background:** Schizophrenia is a lifelong debilitating disease affecting roughly 1% of the population worldwide. Stabilization of symptoms in new patients or patients with an exacerbation of symptoms is critical in improving long term patient outcomes and quality of life. Furthermore, patients who relapse have higher rates of subsequent relapse, incur higher costs of care, and are at risk for undesirable lifetime outcomes. Computer models and simulations have been used to predict health and economic outcomes from a general population perspective and have been used to assist decision making for stakeholders in the care of patients with schizophrenia. Recent efforts have focused on patient-specific characteristics such as symptom scores that provide opportunities to modify disease pathways continuously using complex rule sets.

**Methods:** This study uses a discrete event simulation employing time to event methodology to estimate health and economic outcomes for patients with schizophrenia. The model implements Positive and Negative Symptom Scale scores as a central thread that represents a patient's general disease severity as well as act as a trigger to modify critical parameters. The model was designed such that patients have equal chance of remaining in their initially assigned severity state (mildly ill, moderately ill, severely ill), improve, or worsen over the timeframe of the model. Relapses are defined as a general increase in resource utilization and interaction with healthcare resources and can occur in any setting: in the community or in the hospital. Duration of relapse and time between relapses are scheduled according to disease severity. Costs are calculated assigning units of resources according to the patients health state and setting. The treatment comparators were risperidone standard oral therapy (SOT) and injectable long-acting therapy (LAI) administered monthly. The default time horizon is 5 years.

**Results:** The model predicted that the total cost of care for SOT was $65,409 with patients experiencing a mean number of 4.35 total relapses. Total mean time spent in relapse was 2.12 years. LAI therapy yielded a $2,255 reduction in total costs, 1.19 fewer total relapses, and a reduction of 0.10 years in relapse. More time was spent in the community for the LAI patients than for SOT patients.

**Conclusions:** Computer models implementing time to event methodology using symptom scores as a central mechanism demonstrate the capability to produce credible health and economic outcomes.

**Learning Objectives:**

- To demonstrate understanding of discrete event simulation in the analysis of care for mental health patients.
- To validate symptom scores as a primary driver of simulated mental health outcomes

**Source Of Funding:** #1R43MH082585

**Literature References:**

- NIMH. NIMH Statistics Schizophrenias. Available at: http://www.nimh.nih.gov/statistics/1SCHIZ.shtml. Accessed December 19, 2011.
- Ascher-Svanum H, Zhu B, Faries D, Ernst FR. A comparison of olanzapine and risperidone on the risk of psychiatric hospitalization in the naturalistic treatment of patients with schizophrenia. Ann.Gen.Hosp.Psychiatry. 2004;3(1):11.
- Edwards NC, Rupnow MF, Pashos CL, Botteman MF, Diamond RJ. Cost-Effectiveness Model Of Long-Acting Risperidone in Schizophrenia in the US. Pharmacoeconomics. 2005;23(3):299-314.
- Heeg B, Buskens E, Knapp M, et al. Modelling the treated course of schizophrenia: development of a discrete event simulation model. Pharmacoeconomics. 2005;23 Suppl 1:17-33.

## MAPK14 AND CNR1 GENE VARIANT INTERACTIONS: EFFECTS ON BRAIN VOLUME DEFICITS IN SCHIZOPHRENIA PATIENTS WITH MARIJUANA MISUSE

Obiora E. Onwuameze, MD, PhD, MS

Carver College of Medicine University of Iowa, Iowa City, IA

**Background:** Adolescent marijuana use is associated with increased risk for schizophrenia. We previously reported that marijuana misuse in conjunction with specific cannabinoid receptor 1 (*CNR1*) genetic variants (rs12720071-G-allele carriers) contributed to white matter (WM) brain volume deficits in schizophrenia patients. In this study, we assessed the influence of another cannabinoid-related gene (mitogen-activated protein kinase 14 (*MAPK14*)) as well as potential *MAPK14-CNR1* epistasis in conferring brain volume abnormalities among schizophrenia patients with marijuana abuse/dependence. *MAPK14* encodes a member of the MAPK family involved in diverse cellular processes, including CNR1-induced apoptosis.

**Methods:** We genotyped 235 schizophrenia patients on nine *MAPK14* tag SNPs (tSNPs). Approximately one quarter of the sample had marijuana abuse or dependence. Differential effects of *MAPK14* tSNPs on brain volumes across patients with versus without marijuana abuse/dependence were examined using ANCOVA.

**Results:** Of the *MAPK14* tSNPs, only rs12199654 had significant genotype effects and genotype-by-marijuana misuse interaction effects on WM volumes. rs12199654-A-homozygotes with marijuana abuse/dependence had significantly smaller total cerebral and lobar WM volumes. Effects of *MAPK14*-rs12199654 on WM volume deficits remained significant even after controlling for *CNR1*-rs12720071 genotype. There were significant main effects of *MAPK14-CNR1* diplotype and diplotype-by-marijuana interaction on WM brain volumes with both genetic variants having additive contributions to WM volume deficits only in patients with marijuana misuse.

**Conclusions:** Given that CNR1-induced apoptosis is preceded by increased MAPK phosphorylation, our study suggests that *MAPK14-CNR1*epistatic interactions may mediate brain morphometric features in schizophrenia patients with heavy marijuana use

**Learning Objectives:**

- Significant independent effects of a cannabinoid-related gene (mitogen-activated protein kinase 14 (MAPK14)) on MRI brain morphometry in schizophrenia patients.
- MAPK14-CNR1epistatic interactions may mediate brain morphometric features in schizophrenia patients with heavy marijuana use.

**Source Of Funding:** NIMH Grants MH68380, MH31593, MH40856, MH80128 and MH43271, and Ortho-McNeil Janssen Scientific Affairs.

**Literature References:**

- Andreasen N, et al. (1994). Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA 272, 1763-1769.
- Ho B, et al. (2011a). Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Archives of General Psychiatry 68, 128-137.
- Ho B, et al. (2011b). Cannabinoid receptor 1 gene polymorphisms and marijuana misuse interactions on white matter and cognitive deficits in schizophrenia. Schizophrenia Research 128, 66-75.
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POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## WHICH SCHIZOPHRENIA PATIENTS RELAPSE DESPITE ADHERENCE TO LONG-ACTING ANTIPSYCHOTIC THERAPY?

Henry A. Nasrallah, MD[1], Ibrahim Turkoz, MS[2], Cynthia A. Bossie, PhD[3], Srihari Gopal, MD[2], Larry Alphs, MD, PhD[3], David Hough, MD[2]

[1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Janssen Pharmaceutical Research and Development, LLC, Titusville, NJ, [3]Janssen Scientific Affairs, LLC, Titusville, NJ

**Background:** Schizophrenia is a chronic illness in which most patients have periods of symptom exacerbation and relapse often attributed to nonadherence. However, studies show that a subgroup of patients will relapse despite uninterrupted antipsychotic (AP) long-acting therapy (LAT). An exploratory analysis evaluated a database of subjects with schizophrenia to identify variables that predict relapse despite ensured adherence with LAT.

**Methods:** Post hoc analysis of a 1-year study of risperidone long-acting injection in stable subjects (NCT00297388). Initial Cox proportion hazards regression models explored variables (demographic/clinical) associated with time to relapse. Significance=P<0.05; trend=P<0.10.

**Results:** 59/323 (18.3%) subjects relapsed despite assured continuous AP treatment. Several variables were associated with relapse. Duration of illness: each 1-year increase associated with a 3.3% increase (P=0.002). Prior hospitalizations: >=1 vs 0 associated with a 6.5-fold increase (P=0.064). Age: each 1-year increase associated with a 2.1% increase (P=0.051). PANSS negative symptom score: each 1-point increase associated with a 4.8% decrease (P=0.038). Prior AP dose: high vs low prior dose associated with a 1.8-fold increase (P=0.024). Canada vs US associated with a 2.7-fold increase (P=0.002).

**Conclusion:** Initial results on duration of illness, prior hospitalizations, and age support the need for early implementation of LAT in schizophrenia. Findings suggest patients with a more severe subtype of schizophrenia may have a higher risk of relapse despite guaranteed AP treatment.

**Learning Objectives:**

- To evaluate characteristics associated with relapse in subjects with schizophrenia despite continued antipsychotic treatment
- To educate participants on the characteristics of these patients so they can provide early effective intervention

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

**Literature References:**

- Simpson GM, Mahmoud RA, Lasser RA, Kujawa M, Bossie CA, Turkoz I, Rodriguez S, Gharabawi GM. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry. 2006;67:1194-1203.
- Ciudad A, San L, Bernardo M, Olivares JM, Polavieja P, Valladares A, Gilaberte I. Relapse and therapeutic interventions in a 1-year observational cohort study of nonadherent outpatients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2011, in press.

## EFFICACY OF LURASIDONE IN SCHIZOPHRENIA: FACTOR ANALYSIS OF SHORT-TERM TRIALS

Josephine Cucchiaro, PhD[1], Robert Silva, PhD[1], Yongcai Mao, PhD[1], Antony Loebel, MD[1], Stephen R. Marder, MD[2]

[1]Sunovion Pharmaceuticals Inc., Fort Lee, NJ, [2]Semel Institute for Neuroscience, University of California, Los Angeles, CA

**Objective:** To evaluate the efficacy of lurasidone across 5 validated PANSS factors (positive, negative, disorganized thought, hostility, and depression/ anxiety).

**Method:** A factor analysis was performed post-hoc on combined data from 5 positive, six-week, double-blind, placebo-controlled trials of subjects hospitalized with acute exacerbation of schizophrenia who were randomly assigned to fixed, once-daily doses of lurasidone 40 mg (N=290), 80 mg (N=334), 120 mg (N=290), 160 mg (N=121), or placebo (N=497). Data were analyzed using a mixed model repeated measures (MMRM) model with an unstructured covariance matrix. Effect sizes (ES) were calculated from an ANCOVA analysis (LOCF-endpoint).

**Results:** Baseline characteristics were similar for the combined lurasidone group (N=1035; mean PANSS total score, 96.1) and the placebo group (N=497; mean PANSS total score, 96.1). Treatment with lurasidone was associated with significantly greater improvement in the PANSS total score at Week 6 compared with placebo (LS mean, -22.6 vs. -12.8; P<0.001; ES, 0.42). Significantly greater improvement (P<0.001 for all comparisons) was observed for lurasidone versus placebo across all five PANSS factors at endpoint. Changes for lurasidone vs. placebo were -8.4 vs. -6.0 (ES, 0.35) in the PANSS positive factor; -5.2 vs. -3.3 (ES, 0.32) in the PANSS negative factor; -4.9 vs. -2.8 (ES, 0.40) for the disorganized thought factor; -2.7 vs. -1.6 (ES, 0.34) for the hostility factor; and -3.2 vs. -2.3 (ES, 0.29) on the depression/ anxiety factor. Lurasidone160 mg dose was consistently associated with the highest effect size for each factor.

**Conclusions:** This pooled, post-hoc factor analysis of placebo-controlled trials found that lurasidone, dosed at 40-160 mg daily, was effective in improving all 5 PANSS factors, suggesting efficacy across the spectrum of symptoms associated with schizophrenia.

**Learning Objectives:**

- Understand the importance of multidimensional assessment of outcome in schizophrenia
- Be knowledgeable about the efficacy of lurasidone for the treatment of the full spectrum of schizophrenia symptoms

**Source Of Funding:** Funded by Sunovion Pharmaceuticals Inc.

**Literature References:**

- Marder SR et al. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538-46.
- Emsley R et al. The factor structure of the PANSS in recent-onset psychosis. Schizophr Res 2003;61:47-57.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## LONG-TERM SAFETY AND TOLERABILITY OF ONCE-MONTHLY ARIPIPRAZOLE INTRAMUSCULAR DEPOT (ARI-IM-DEPOT) FOR MAINTENANCE TREATMENT IN SCHIZOPHRENIA

Wolfgang Fleischhacker, MD[1], Raymond Sanchez, MD[2], Pam Perry, MS[2], Na Jin, MS[2], Brian Johnson, MS[2], Robert A. Forbes, PhD[2], Robert M. McQuade, PhD[2], William H. Carson, MD[2], John Kane, MD[3]

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**Objective:** To understand the safety and tolerability profile of aripiprazole intramuscular depot (ARI-IM depot) during maintenance treatment of schizophrenia.

**Methods:** Patients requiring chronic treatment with an antipsychotic were eligible and patients not already on aripiprazole monotherapy were cross-titrated during weekly visits from other antipsychotic(s) to oral aripiprazole monotherapy during the 4–6 weeks oral conversion phase (Phase 1). All patients requiring chronic treatment with an antipsychotic entered a 4–12-week oral stabilization phase (Phase 2) and received oral aripiprazole (10–30 mg/day). Patients meeting stability criteria for 4 weeks then entered an intramuscular depot stabilization phase (Phase 3), wherein they received ARI-IM-depot injections every 4 weeks (400 mg, single decrease to 300 mg permitted) with co-administration of aripiprazole oral tablets in the first 2 weeks. Patients meeting stability criteria for 12 consecutive weeks were randomized (2:1) to ARI-IM-depot or placebo during a 52-week, double-blind maintenance phase (Phase 4). Safety of treatment was assessed across the study phases by time of first onset of adverse events (AEs), changes in movement disorder rating scales and changes in weight and metabolic parameters.

**Results:** The study was stopped early because efficacy was demonstrated by the preplanned interim analysis (conducted after 64 relapses). ARI-IM-depot was well tolerated with similar rates of AEs across all phases. Discontinuations due to treatment-emergent AEs were: Phase 1, 3.8% (24/632); Phase 2, 3.0% (21/709); Phase 3, 4.9% (n=28/576); Phase 4, 7.1% (n=19/269). Most AEs were mild or moderate; severe AEs were rare (<5.0% incidence in all phases). AEs >5% incidence in any phase were: insomnia (all phases); headache (Phases 1, 3 and 4); anxiety, akathisia, weight increase (Phase 3 and 4); injection site pain (Phase 3); and tremor (Phase 4). The majority of AEs (headache, somnolence, nausea) had a peak first onset within the first 4 weeks of treatment. The incidence of treatment-emergent extrapyramidal symptoms (EPS) and EPS-related events was similar in all phases (Phase 4 ARI-IM-depot 14.9% vs. placebo 9.7%). Mean baseline weight in each phase was similar (range 80.4–84.8 kg). Mean changes in weight from baseline were Phase 1: –0.2 kg; Phase 2: 0.1 kg; Phase 3: –0.2 kg; and Phase 4 (ARI-IM-depot vs. placebo): –0.2 vs. –0.4 kg. There were no unusual shifts in laboratory values or fasting metabolic parameters across all study phases. Shifts from normal to high metabolic values occurred at similar low rates between ARI-IM-depot and placebo in the double blind phase.

**Discussion:** No unexpected AEs emerged during the transition to ARI-IM-depot, or with long-term ARI-IM-depot. Rates of AEs in Phase 1 were no different than rates in Phase 2, suggesting that the study switch strategy was useful. These data suggest that ARI-IM-depot offers a new option with a different risk–benefit profile than currently available treatments.

**Learning Objectives:**

- To understand the long-term safety and tolerability of ARI-IM-depot for maintenance treatment in schizophrenia produced no unexpected adverse events (AEs)
- To understand the incidence of AEs during the oral conversion and stabilization phases were similar as well as during the IM depot stabilization and maintenance phases
- To understand the AE profile of ARI-IM-depot in the long-term maintenance treatment of schizophrenia

**Source Of Funding:** Otsuka Pharmaceutical Development and Commercialization, Inc.

## FACTORS AFFECTING PLACEBO SEPARATION IN A CLINICAL TRIAL FOR COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Michael Hufford, PhD[1], Maria Gawryl, PhD[2], Nancy Dgetluck, PhD[2], Vicki Davis, PhD[1], Stephen Murray, MD[2], Richard Keefe, PhD[1,3], Dana Hilt, MD[2]

[1]NeuroCog Trials, Durham, NC, [2]EnVivo Pharmaceuticals, Watertown, MA, [3]Duke University, Durham, NC

Placebos, far from being inert substances, are comprised of a host of potent social, psychological, and learning stimuli that are capable of producing symptomatic improvements in nearly all areas of CNS research (e.g., Benedetti et al., 2011). A variety of methodological issues can significantly impact the placebo response among patients with schizophrenia (e.g., Mallinckrodt et al., 2011). We examined methodological issues affecting placebo separation in a clinical trial of EVP-6124, a selective, potent, oral nicotinic alpha-7 agonist being developed for cognitive impairments in schizophrenia. A Phase 2b trial evaluated the safety and efficacy of two doses of EVP-6124 (0.3 mg and 1.0 mg qd) versus placebo among 319 chronic schizophrenia patients on stable second-generation antipsychotic drugs enrolled in the U.S., Russia, Ukraine and Serbia. Each patient was treated for 3 months. EVP-6124 was safe, well tolerated, and had clinically meaningful effects compared to placebo on cognitive performance (CogState and MATRICS Consensus Cognitive Battery [MCCB- in US subjects only]) and interview-based assessments (Schizophrenia Cognition Rating Scale [SCoRS]) as well as negative symptoms. We explored the temporal patterning of responses on the MCCB by examining what percentage of total change had occurred at the Day 44 vs. Day 84 visit. Placebo patients manifested 94% of their total change by the Day 44 visit, compared to only 60% and 56% for the 0.3 and 1.0 mg EVP-6124 groups, respectively. In short, nearly all of the placebo effect's total impact on the MCCB was detected by Day 44, whereas both EVP-6124 groups continued to show substantial cognitive improvements in the latter half of the trial. We also examined whether the presence of an informant would help to provide a more sensitive test of cognitive impairments on the SCoRS. Consistent with previous research, we found that the presence of an informant helped to increase the effect sizes (ES) (1.0 mg EVP-6124 subjects vs. placebo with no informant: ES = .36; with an informant: ES = .51). These findings have important methodological implications for the design and conduct of future clinical trials of cognitive enhancing agents in schizophrenia.

**Learning Objectives:**

- Review the roles that a variety of methodological factors play in signal detection in clinical trials of cognitive impairments in patients with schizophrenia
- Describe at least two methodological implications of this research in terms of future clinical trial design

**Source Of Funding:** EnVivo Pharmaceuticals

**Literature References:**

- Benedetti, F, Carlino, E, Pollo, A: How placebos change the patient's brain. Neuropsychopharm Rev 2011; 36:339-354.
- Mallinckrodt CH, Tamura, RN, Tanaka, Y: Recent developments in improving signal detection and reducing placebo response in psychiatric clinical trials. J Psych Res 2011; 45:1202-1207.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## PATIENT-REPORTED OUTCOMES WITH ARIPIPRAZOLE INTRAMUSCULAR DEPOT (ARI-IM-DEPOT) FOR LONG-TERM MAINTENANCE TREATMENT IN SCHIZOPHRENIA

Raymond Sanchez, MD[1], Brian Johnson, MS[1], Na Jin, MS[1], Robert A. Forbes, PhD[1], William H. Carson, MD[1], Robert McQuade, PhD[1], John M. Cane, MD[2], Wolfgang Fleischhacker, MD[3]

[1]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, [2]Zucker Hillside Hospital and The Hofstra North Shore-LIJ School of Medicine, Glen Oaks, NY, [3]Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria

**Objective:** To characterize the adherence profile of ARI-IM-depot by examining patient-reported outcomes from a long-term treatment trial of patients (pts) with schizophrenia.

**Methods:** Pts requiring chronic treatment with an antipsychotic were eligible. Pts not already on ARI monotherapy were cross-titrated during weekly visits from other antipsychotic(s) to oral ARI monotherapy during a 4–6-week oral conversion phase (Phase 1). Subjects entered a 4–12-week oral stabilization phase (Phase 2) and received oral ARI (10–30 mg/day). Subjects meeting stability criteria for 4 weeks then entered an intramuscular depot stabilization phase (Phase 3) in which they received 400 mg ARI-IM-depot injections every 4 weeks (single decrease to 300 mg permitted) with co-administration of oral ARI oral tablets in the first 2 weeks. Subjects meeting stability criteria for 12 consecutive weeks were randomized (2:1) to ARI-IM-depot or placebo during a 52-week, double-blind maintenance phase (Phase 4). Mean changes in patient-reported outcomes were assessed from baseline to last visit in Phases 2–4 using the Drug Attitude Inventory (DAI)[1], Medication Adherence Questionnaire (MAQ)[2], and the Patient Satisfaction with Medication Questionnaire (PSMQ) modified[3].

**Results:** 710 pts entered oral stabilization (633 of which had been titrated to oral ARI during Phase 1); 576 progressed to intramuscular depot stabilization and 403 pts were randomized to double-blind treatment. The study was stopped early because efficacy was demonstrated by the pre-planned interim analysis (conducted after 64 relapses). Between Phases 2–4 mean DAI scores remained similar across phases (Phase 2, 21.5; Phase 3, 21.4; Phase 4, 21.1 ARI-IM-depot vs. 22.2 placebo) indicating a positive (adherent) attitude towards medication. Mean MAQ scores were between 0–1 indicating high adherence behavior. PSMQ scale scores were assessed for Phases 3–4 and showed that the percentage of pts with high levels of treatment satisfaction between baseline and last visit, respectively, was Phase 3: 97.0% vs. 92.8%; Phase 4 ARI-IM-depot: 97.0% vs. 92.7%; Phase 4 placebo: 96.2% vs. 85.0%. The percentage of pts with a preference for the current medication between baseline and last visit, respectively, was also high (Phase 3: 93.4% vs. 89.1; Phase 4 ARI-IM-depot: 94.8% vs. 86.2%; Phase 4 placebo: 97.7% vs. 85.7%). Finally, there was a sustained percentage of pts reporting less to no side-effects between baseline and last visit, respectively, Phase 3: 88.0% vs. 86.9%; Phase 4 ARI-IM-depot: 90.3% vs. 88.9%; Phase 4 placebo: 92.6% vs. 89.0%.

**Discussion:** ARI-IM-depot offers a new treatment option for the long-term management of schizophrenia with the potential to improve adherence to medication resulting from improved patient-reported outcomes and medication satisfaction.

**Learning Objectives:**

- To understand the effect of long-term (up to 52 weeks) administration of ARI-IM-depot for the treatment of schizophrenia on patient-reported outcomes
- To understand the impact of long-term stability of medication on patient-reported outcomes

**Source Of Funding:** Otsuka Pharmaceutical Development and Commercialization, Inc.

**Literature References:**

- Hogan T, et al. Psychol Med 1983;13:177–183.
- Morisky D, et al. Med Care 1986;24:67–74.
- Kalali A. Curr Med Res Opin 1999;15:135–137.

## EFFICACY OF ARIPIPRAZOLE INTRAMUSCULAR DEPOT (ARI-IM-DEPOT) FOR THE LONG-TERM MAINTENANCE TREATMENT OF SCHIZOPHRENIA

John M. Kane, MD[1], Raymond Sanchez, MD[2], Pam Perry, MS[2], Na Jin, MS[2], Brian Johnson, MS[2], Robert A. Forbes, PhD[2], Robert D. McQuade, PhD[2], William H. Carson, MD[2], Wolfgang Fleischhacker, MD[3]

[1]The Zucker Hillside Hospital and The Hofstra North Shore-LIJ School of Medicine, Glen Oaks, NY, [2]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, [3]Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria

**Objective:** To evaluate the efficacy and tolerability of once-a-month aripiprazole intramuscular depot (ARI-IM-depot), a dopamine partial agonist, for maintenance treatment in adults with schizophrenia.

**Methods:** Patients requiring chronic treatment with an antipsychotic were eligible and patients not already on aripiprazole monotherapy were cross-titrated during weekly visits from other antipsychotic(s) to oral aripiprazole monotherapy during the 4–6 weeks oral conversion phase (Phase 1). All patients entered a 4–12-week oral stabilization phase (Phase 2) and received oral aripiprazole (10–30 mg/day). Patients meeting stability criteria for 4 weeks then entered an intramuscular depot stabilization phase (Phase 3), wherein they received ARI-IM-depot injections every 4 weeks (400 mg, single decrease to 300 mg permitted) with co-administration of oral aripiprazole tablets in the first 2 weeks. Patients meeting stability criteria for 12 consecutive weeks were randomized (2:1) to ARI-IM-depot or placebo during a 52-week, double-blind maintenance phase (Phase 4). The primary endpoint was time to impending relapse. Safety and tolerability were also assessed.

**Results:** Of 710 patients who entered the oral stabilization phase, 576 progressed to ARI-IM-depot stabilization and 403 patients were randomized to double-blind, placebo-controlled treatment. The study was stopped early because efficacy was demonstrated by the preplanned interim analysis (conducted after 64 relapses). Time-to-impending relapse was significantly delayed in ARI-IM-depot compared with placebo in both interim and final analyses ($p<0.0001$, log-rank test). The rate of impending relapse was significantly lower with ARI-IM-depot than placebo at endpoint (final analysis 10.0%, n=27/269 vs. 39.6%, n=53/134; hazard ratio [HR], 5.0; 95% confidence interval [CI], 3.15–8.02, $p<0.0001$). Improvements in Positive and Negative Syndrome scale (PANSS) Total score were maintained with ARI-IM-depot treatment but showed significant worsening with placebo (mean change at Week 52: PANSS, ARI-IM-depot = 1.4, placebo = 11.6, $p<0.0001$). Additionally, Clinical Global Impression of Severity scores showed significant differences favoring ARI-IM-depot ($p<0.0001$). The most common treatment-emergent adverse events (AEs; occurring ≥5% of aripiprazole-treated patients and greater than placebo) were insomnia (10.0% vs. 9.0%), tremor (5.9% vs. 1.5%), and headache (5.9% vs. 5.2%), respectively. Most AEs were mild or moderate in severity. The incidence of injection site pain in the ARI-IM-depot stabilization phase was 5.9%, while in the ARI-IM-depot maintenance phase was, respectively, 3.0% vs. 3.7% for ARI-IM-depot compared with placebo.

**Conclusions:** ARI-IM-depot significantly delayed time to impending relapse compared with placebo and was a well-tolerated maintenance treatment option in schizophrenia.

**Learning Objectives:**

- To understand the Phase III study design employed to assess the efficacy and safety profile of a new long-acting, once-a-month, intramuscular formulation of ARI-IM-depot
- To show that ARI-IM-depot significantly delays time to impending relapse compared with placebo
- To understand that long-acting, once-a-month ARI-IM depot was well tolerated for the maintenance treatment of schizophrenia

**Source Of Funding:** Otsuka Pharmaceutical Development and Commercialization, Inc.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## ADJUNCTIVE LISDEXAMFETAMINE DIMESYLATE TREATMENT OF PREDOMINANT NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: POST HOC ANALYSIS BY GLOBAL IMPROVEMENT CRITERIA

Jean-Pierre Lindenmayer, MD[1], Bryan Dirks, MD[2], Henry Nasrallah, PhD[3], Courtney Kirsch, BS[2], Ben Adeyi, MS[2], Brian Scheckner, PharmD[2], Robert Lasser, MD[2]

[1]New York University School of Medicine, New York, NY, [2]Shire Development Inc., Wayne, PA, [3]University of Cincinnati College of Medicine, Cincinatti, OH

**Objective:** To examine adjunctive lisdexamfetamine dimesylate (LDX) effects in adults with predominant negative symptoms of schizophrenia (NSS) relative to baseline characteristics and global improvement.

**Methods:** Stable outpatients with NSS on atypical antipsychotics received open-label (OL) LDX for 10 weeks. Eligible participants (any SANS-18 improvement at week 10) entered a 4-week, double-blind, placebo-controlled randomized withdrawal (RW; week 10-14). Efficacy measures included SANS-18 (primary) and PANSS subscales. Post hoc analysis examined response to LDX by Clinical Global Impressions-Change (CGI-C) ratings of </=2 (very/much improved), =3 (minimally improved), or =4 (no change) at week 10 and exploratory regression analysis of predictors of CGI-C ratings </=2. Safety analysis included treatment-emergent adverse events (TEAEs).

**Results:** 92 participants received OL LDX; 21, 49, and 17 with CGI-C ratings </=2, =3, or =4 at week 10 were analyzed here. Mean change (95% CI) in SANS-18 score (week 0-10) was −12.9 (−15.0, −10.80) overall and −23.5 (−28.1, −18.8), −11.6 (−13.8, −9.4), and −4.6 (−7.0, −2.3) for CGI-C ratings </=2, =3, or =4. PANSS positive score decreased slightly overall (P<.0001) and for CGI-C ratings </=2 (P=.0068) and =3 (P=.0039), but not =4 (P=.2636). Multivariate analysis of CGI-C rating </=2 predictors showed odds ratio (95% CI) of 3.6 (1.41, 8.95) for female gender. TEAEs were reported in 60.9% overall during OL and in 32.4% on LDX and 20.0% on placebo during RW.

**Conclusion:** The addition of LDX to stable, medicated participants with schizophrenia, improved NSS without increasing positive symptoms. Exploratory, post hoc analysis suggested female gender may be one of the predictors of good response to LDX.
Clinical research was funded by the sponsor, Shire Development Inc.

**Learning Objectives:**

- Improvement in negative symptoms of schizophrenia (NSS) with adjunctive lisdexamfetamine dimesylate in relation to global improvement
- Contribution of baseline characteristics to improvements in NSS relative to the highest level of global improvement

**Source Of Funding:** Clinical research was funded by the sponsor, Shire Development Inc.

**Literature References:**

- Foussias G, Remington G: Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull 2010; 36:359-369.
- Hanson E, Healey K, Wolf D, Kohler C: Assessment of pharmacotherapy for negative symptoms of schizophrenia. Curr Psychiatry Rep 2010; 12:563-571.

## LURASIDONE VS. QUETIAPINE XR FOR RELAPSE PREVENTION IN SCHIZOPHRENIA: A 12-MONTH, DOUBLE-BLIND STUDY

Antony Loebel, MD[1], Josephine Cucchiaro, PhD[1], Jane Xu, PhD[1], Kaushik Sarma, MD[1], Andrei Pikalov, MD, PhD[1], John M. Kane, MD[2]

[1]Sunovion Pharmaceuticals Inc., Fort Lee, NJ, [2]Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, NY

**Objectives:** To evaluate the long-term maintenance of antipsychotic efficacy of lurasidone (LUR) compared with quetiapine XR (QXR) in subjects with schizophrenia who have demonstrated clinical response to an initial 6 weeks of treatment with either LUR or QXR, as measured by the time to relapse of psychotic symptoms.

**Methods:** After completing an initial double-blind, placebo-controlled, 6 week trial with LUR or QXR, subjects were eligible to receive 12 months of double-blind, flexible once-daily doses of LUR (40-160 mg) vs. QXR (200-800 mg). The primary *a priori* efficacy comparison was between subjects treated with LUR (n=139) and QXR (n=79) who were clinical responders after acute treatment. The primary endpoint, time-to-relapse, was analyzed using a Cox proportional hazards model, with a pre-specified non-inferiority margin for the risk of relapse hazard ratio of 1.93.

**Results:** LUR was non-inferior to QXR in risk for relapse over the 12 month treatment period (hazard ratio 0.728, 95% CI [0.410, 1.295]). Relapse risk for LUR treated subjects was 27.2% lower than for those treated with QXR. The Kaplan-Meier estimate of the probability of relapse at 12 months was lower for LUR vs. QXR (0.237 vs. 0.336). Rates of adverse events ≥5% on LUR were akathisia (12.6%), headache (10.6%), insomnia (7.9%), anxiety (6.0%), parkinsonism (6.0%), and weight increased (6.0%). Analysis of changes from acute study baseline to 12 months of treatment (OC) with LUR and QXR, respectively, showed a mean change in weight of +0.7 vs. +1.2 kg; a median change in glucose of +1.0 vs. +1.0 mg/dL; a median change in cholesterol of 0.0 vs. +4.0 mg/dL; and a median change in triglycerides of -18.0 vs. -7.0 mg/dL.

**Conclusions:** This long-term, double-blind study demonstrated non-inferiority of lurasidone to QXR in prevention of relapse over a 12 month period, with a 27.2% reduction in relapse risk compared with QXR. In the current study, up to 12 months of treatment with lurasidone was found to be safe and well-tolerated, with minimal adverse effects on metabolic parameters, and a minimal effect on weight.

**Learning Objectives:**

- Understand the importance of maintenance therapy for preventing relapse in schizophrenia
- Be knowledgeable about the relapse prevention efficacy of lurasidone and quetiapine XR

**Source Of Funding:** Funded by Sunovion Pharmaceuticals Inc.

**Literature References:**

- Meltzer HY et al. Lurasidone in the treatment of schizophrenia. Am J Psychiatry 2011;168:957-67.
- Kishimoto T et al. Relapse prevention in schizophrenia: a systematic review and meta-analysis. Mol Psychiatry. 2011 Nov 29. doi: 10.1038/mp.2011.143.

POSTER SESSION 2
12:30 P.M. - 2:15 P.M.

## EFFECTS OF A LONG-ACTING INJECTABLE FORMULATION OF ARIPIPRAZOLE ON SECONDARY EFFICACY OUTCOMES IN MAINTENANCE TREATMENT OF SCHIZOPHRENIA

William H. Carson, MD[1], Pam Perry, BS[1], Raymond Sanchez, MD[1], Na Jin, MS[1], Robert A. Forbes, PhD[1], Robert McQuade, PhD[1], Wolfgang Fleischhacker, MD[2], John Kane, MD[3]

[1]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, [2]Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria, [3]Zucker Hillside Hospital and The Albert Einstein College of Medicine, Glen Oaks, NY

**Objective:** To evaluate the secondary efficacy outcomes from a clinical trial of a once-monthly intramuscular depot formulation of aripiprazole (ARI-IM-depot) as maintenance treatment in adults diagnosed with schizophrenia.

**Methods:** Patients requiring chronic treatment with an antipsychotic were eligible and patients not already on aripiprazole monotherapy were cross-titrated during weekly visits from other antipsychotic(s) to oral aripiprazole monotherapy during a 4–6-week oral conversion phase (Phase 1). All patients entered a 4–12-week oral stabilization phase (Phase 2) and received oral aripiprazole (10–30 mg/day). Patients meeting stability criteria for 4 weeks then entered an intramuscular depot stabilization phase (Phase 3), wherein they received ARI-IM-depot injections every 4 weeks (400 mg, single decrease to 300 mg permitted) with co-administration of oral aripiprazole tablets in the first 2 weeks. Patients meeting stability criteria for 12 consecutive weeks were randomized (2:1) to ARI-IM-depot or placebo during a 52-week, double-blind maintenance phase (Phase 4). Secondary efficacy assessments included mean changes in the Personal and Social Performance (PSP) scale scores, mean changes in Positive and Negative Syndrome Scale (PANSS) positive and negative scores and mean change in the Investigator's Assessment Questionnaire (IAQ) scores, a scale designed to evaluate response to antipsychotics.

**Results:** Seven-hundred-ten patients entered oral stabilization, 576 progressed to ARI-IM-depot stabilization and 403 patients were randomized to double-blind treatment. The study was stopped early because efficacy was demonstrated by the preplanned interim analysis (conducted after 64 relapses). Mean changes in PSP scale scores (last observation carried forward [LOCF]) showed improvement during the oral (3.0) and ARI-IM-depot stabilization (2.6) phases. Mean change in PSP scores during double-blind treatment showed greater functional stability with ARI-IM-depot (−1.7) than placebo (−6.2) (p=0.0002 vs. placebo). Mean PANSS Positive and Negative subscale scores (LOCF) improved during the oral (−2.1 and −1.2, respectively) and ARI-IM-depot (−1.0 and −1.2) stabilization phases. Mean change during double-blind treatment in PANSS Positive (Week 52 LOCF, 0.4 vs. 4.3; p<0.0001) and Negative (Week 52 LOCF, 0.2 vs. 1.6; p<0.0001) subscale scores all showed symptom stability with ARI-IM-depot treatment but showed significant worsening with placebo. Mean IAQ Total score also remained stable (Phase 2, 31.3; Phase 3, 30.6). During double-blind treatment, the mean change was +1.3 for ARI-IM-depot vs. +3.8 for placebo (p<0.0001).

**Conclusions:** Improvements in symptoms, functioning and overall response to treatment were achieved during stabilization and maintained in patients during Phase 4. ARI-IM-depot, thus, offers a new option for maintenance therapy of schizophrenia with a different risk–benefit profile than currently available treatments.

**Learning Objectives:**

- To understand the efficacy profile of a new long-acting once-a-month intramuscular formulation of aripiprazole (ARI-IM-depot)
- To understand the efficacy of ARI-IM-depot across a range of symptoms in schizophrenia

**Source Of Funding:** Otsuka Pharmaceutical Development and Comercialization, Inc.

## ASSESSMENT OF CHANGE IN BODY WEIGHT AFTER ANTIPSYCHOTIC TREATMENT IS CONFOUNDED BY REGRESSION TO THE MEAN

Cynthia Siu, PhD[1], Jane Xu, PhD[2], Josephine Cucchiaro, PhD[2], Andrei Pikalov, MD, PhD[2], Antony Loebel, MD[2]

[1]Data Power (DP), Inc., Ringoes, NJ, [2]Sunovion Pharmaceuticals Inc., Fort Lee, NJ

**Objective:** The aim of this post-hoc analysis was to examine whether the previously observed correlation between initial BMI range and subsequent weight change reflected in part a statistical artifact, regression to the mean (RTM), rather than true effect modification (Allison et al., 2009).

**Methods:** Body weight and BMI were measured at baseline and at the 6-week endpoint in a double-blind, placebo- and active-controlled trial of lurasidone (LUR) and olanzapine (OLZ). Regression analysis was applied to estimate the magnitude of bias due to RTM on measurement of change in body weight at Week 6. To correct for the RTM bias, a control group was used in the ANCOVA model to estimate differences in weight change between treatment groups by baseline BMI ranges, using a statistical interaction test.

**Results:** Among placebo subjects, the magnitude of RTM bias in the obese subgroup (baseline BMI >=30) was -5 kg at week 6, due to a non-perfect correlation between baseline BMI and Week-6 measurements of body weight (r=0.87 < 1) and non-random selection (median baseline weight for the obese subgroup was 34.8 kg or 9 kg above the placebo group mean of 25.7 kg). A similar magnitude of RTM bias (-4 kg) was observed in the subgroup of obese subjects in both the olanzapine and lurasidone treatment groups. Compared to placebo, weight changes in the baseline obese, overweight, and normal groups were +4.4 kg, +5.3 kg, and +2.7 kg, respectively, for olanzapine-treated subjects (treatment-by-baseline BMI interaction tests, p=0.09); and +0.40 kg, +0.02 kg, and +0.68 kg, respectively, for lurasidone-treated subjects (treatment-by-baseline BMI interaction tests, p=0.72).

**Conclusions:** Contrary to previous findings, we found no evidence in this analysis supporting the argument that the magnitude of drug-induced weight gain was less in subjects with higher initial BMI than those subjects with average or low baseline BMI. Our findings suggest the previously observed inverse relationship between baseline BMI and weight change following antipsychotic treatment reflects, in part, RTM bias. Antipsychotic drugs appear to cause similar weight change in both high and low baseline BMI groups, when an appropriate control is incorporated in treatment comparisons.

**Learning Objectives:**

- To better understand the effect of initial BMI on drug-induced weight changes
- To further understanding of regression to mean bias, a statistical artifact

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

**Literature References:**

- Allison DB; Loebel AD; Lombardo I; Romano SJ; Siu CO: Understanding the relationship between baseline BMI and subsequent weight change in antipsychotic trials: effect modification or regression to the mean? Psychiatry Res. 2009; 170:172-6.
- Yudkin PL; Stratton IM: 1988. How to deal with regression to the mean in intervention studies. Lancet 1988; 347:241–243.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## AN EVALUATION OF THE PSYCHOMETRIC PROPERTIES OF THE BRIEF NEGATIVE SYMPTOM SCALE (BNSS) IN INDIVIDUALS WITH SCHIZOPHRENIA

Gregory P. Strauss, PhD[1], Lauren A. Catalano, BS[1], James M. Gold, PhD[1], William R. Keller, MD[1], Robert W. Buchanan, MD[1], William T Carpenter, MD[1], Brian Kirkpatrick, MD[2]

[1]University of Maryland School of Medicine, Baltimore, MD, [2]Texas A&M College of Medicine, Temple, TX

The NIMH-MATRICS Consensus Statement on Negative Symptoms recommended the development of a next-generation negative symptom assessment that measures the domains of blunted affect, alogia, asociality, anhedonia, and avolition. The Brief Negative Symptom Scale (BNSS) was designed to measure symptoms in relation to these domains and is well-suited for use in clinical trials and other studies examining negative symptoms. In the current study, we examined the psychometric properties of the BNSS in a new sample of 62 individuals with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Similar to our initial published study on the measure, the internal consistency of the BNSS total score was excellent (0.94) and the alpha coefficients ranged from 0.93 to 0.95 when each item was omitted individually, suggesting no benefit from excluding any individual items. Comparisons with measures of positive symptoms, disorganization, other negative symptom instruments, a functional outcome measure, and neuropsychological functioning on the MATRICS Cognitive Consensus Battery supported the discriminant and concurrent validity of the scale. Thus, the BNSS demonstrates good reliability and validity, and may be of considerable interest for use in clinical trials because of its brevity, ease of use and training, and coverage of the 5 domains identified in the MATRICS Consensus Conference.

**Learning Objectives:**

- To identify the 5 domains of negative symptoms considered integral at the MATRICS conference
- To evaluate the psychometric properties of the BNSS instrument

**Source Of Funding:** K23-MH092530 to Dr. Strauss and R01-MH080066 to Dr. Gold.

**Literature References:**

- Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006;32:214–219.
- Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.F., Daniel, D., Cienfuegos, A., Marder, S.R. (2011). The Brief Negative Symptom Scale: Psychometric Properties. Schizophrenia Bulletin, 37, 300-305.

## THE EVALUATION OF NEGATIVE SYMPTOMS BY VIDEOCONFERENCING IN A CLINICAL TRIAL

Janet B.W. Williams, PhD[1,2], Danielle Popp, PhD[1], Douglas A. Osman, PhD[1], Elan A. Cohen, PhD[1], Michael J. Detke, MD, PhD[1,3]

[1]MedAvante, Inc., Hamilton, NJ, [2]Department of Psychiatry, Columbia University, New York, NY, [3]Indiana University School of Medicine, Indianapolis, IN

**Background:** Negative syndromes in Schizophrenia are of increasing interest to drug developers, and several assessment strategies have emerged for identifying negative symptoms. Among these is the Negative Symptom Assessment (NSA-16), as well as the PANSS negative symptom subscale and the Marder subscale. Assessment of patients with schizophrenia by videoconferencing has been shown to yield results equivalent to those obtained when the scale is administered face-to-face. Advantages of remote assessment include blinding to protocol details and visit number, effectively eliminating enrollment and expectation biases. Videoconferencing can also be used to facilitate calibration of a global cohort of raters, as interviews can be observed "live" by remote trainers. Examination of the ability to assess negative symptom scales reliably by videoconferencing is timely.

**Methods:** The PANSS and the NSA-16 were administered to subjects with schizophrenia in a randomized clinical trial via live videoconferencing by blinded independent central raters. Subjects were interviewed at screen, at 11 more visits over 36 weeks, and at endpoint or 1 year. On a subset of subjects, a senior clinician observed and independently rated the PANSS and NSA as a quality control measure.

**Results:** The PANSS and NSA-16 were administered at all visits (n=1127) to 224 subjects by 17 different blinded independent central raters. The mean duration of the NSA was 16 min. (SD=7); each followed a PANSS that was on average 36 min. (SD = 15). All total and subscale scores were normally distributed at screening. ICCs between raters and observing trainers were .98 on the NSA total score (N = 65 pairs) and .96 on the PANSS total score (N = 69 pairs). ICCs of individual NSA items ranged from .72-1.0, with a mean ICC of .91. ICCs of PANSS subscales ranged from .94 -.96 with ICCs of .95 for the Marder subscale and .94 for the negative subscale. Inter-item correlations for the NSA and Marder subscale will be presented as well as relationships between items measuring similar constructs across the two scales.

**Conclusion:** Excellent item-level ICCs for the NSA suggest that negative symptoms can be rated reliably by videoconferencing using well-calibrated blinded independent raters.

**Learning Objectives:**

- Better understand the evaluation of negative symptoms of Schizophrenia by videoconferencing
- Learn about the psychometrics of the NSA

**Source Of Funding:** MedAvante, Inc.

**Literature References:**

- Alphs LD, Summerfelt A, Lann H, Muller RJ: The negative symptom assessment: A new instrument to assess negative symptoms of schizophrenia. Psychopharmacol Bull 1989;25(2):159-63.
- Sharp IR, Kobak KA, Osman DA: The use of videoconferencing with patients with psychosis: a review of the literature. Ann Gen Psychiatry 2011;10(14).

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## RELIABILITY OF THE GLOBAL ASSESSMENT OF FUNCTIONING SCALE IN PATIENTS WITH EXCESSIVE SLEEPINESS ASSOCIATED WITH SHIFT WORK DISORDER

Christian Yavorsky, PhD[1], Anzalee Khan, PhD[2], Mark Opler, PhD[3], Guillermo DiClemente, PhD[4], Brian Rothman, PhD[5], Ashleigh DeFries, MS[5], Sofija Jovic, PhD[5]

[1]Cronos Clinical Consulting Services, Hamilton, NJ, [2]Nathan S. Kline Institute for Psychiatric Research, New York, NY, [3]New York University School of Medicine, New York, NY, [4]Cronos Consulting Services, Hamilton, NJ, United Kingdom, [5]Prophase LLC, New York, NY

**Background:** The Global Assessment of Functioning Scale (GAF) is widely used to assess psychological, social and occupational functioning. The GAF scale identifies the lowest and highest levels for a hierarchy of an illness. After the introduction of the GAF, a number of studies have been published that claim the GAF to be a reliable scale, but these studies have all been conducted in research settings and have not been studied in patients with excessive sleepiness associated with shift work disorder. Additionally, the GAF lacks structure and depends greatly upon clinical judgment and conjecture. The directions on the GAF do not explicitly state how to integrate the three areas of functioning into a single composite rating.

**Objectives:** In view of the lack of studies on the GAF in patients with shift work disorder (SWD), the objective of this study was to assess the reliability of the GAF in a sample of outpatients with SWD in a clinical trial setting where the GAF is part of the outcome measure. We aimed to discover whether the GAF meets its purposes, when used in SWD, after a comprehensive training and structured guidelines was implemented.

**Methods:** Data was obtained from a Phase IV randomized placebo controlled clinical trial for 382 patients with clinically diagnosed shift work disorder. For this secondary analysis, only pre-treatment (screening and baseline) GAF scores are assessed as the aim of the study is to assess reliability and present baseline characteristics according to tertiles (low, medium, high scores) of the GAF in patients with SWD. Patients included in the study experienced late-in-shift sleepiness between 4 AM and 8 AM and were functionally impaired (Global Assessment of Functioning <70).

**Results:** At screening, the mean GAF score by the clinician was 62.99 (SD: 4.48) and ranged from 46 to 70. The mean GAF score at baseline (1 week apart) was 62.78 (SD: 4.34) and ranged from 50 to 70. There were no signiﬁcant differences across study sites. Pearson's correlation coefficients between the baseline GAF score and the screening GAF score was 0.895 ($P \leq 0.001$). Similarly, the concordance seen by Cohen's Kappa between the GAF score at screening and at baseline when using categories (low ≤ 50, moderate 51 – 55, high ≥ 56) was statistically signiﬁcant (kappa = .16, p = 0.03). Internal consistency between screening and baseline was also high with Cronbach alpha of 0.944.

**Conclusions:** The results of this study present new findings that the GAF can be rated reliably when used with mild-to-moderately impaired patients with SWD and when presented with specific guidelines for rating the GAF. Current guidelines for rating GAF are not comprehensive. Theoretical and empirical studies, as well as development of a manual with more information about scoring the GAF for various populations are warranted.

**Learning Objectives:**

- The poster presentation will help readers understand the use of the GAF in shift work disorder
- Readers will learn to analyze the role of the GAF scale in vulnerable populations, not previously explored
- Understand the current state of knowledge regarding the GAF scale as studied in large practical clinical trial
- The poster will demonstrate advantages and disadvantages of the GAF including novel approaches to administering the GAF with structured training

**Source Of Funding:** Funding was not obtained for this study

**Literature References:**

- Aas IH. Guidelines for rating Global Assessment of Functioning (GAF). Ann Gen Psychiatry. 2011 Jan 20;10:2.
- Ramirez A, Ekselius L, Ramklint M. Axis V - Global Assessment of Functioning scale (GAF), further evaluation of the self-report version. Eur Psychiatry. 2008 Dec;23(8):575-9.

## LAMOTRIGINE DOSING FOR PREGNANT PATIENTS WITH BIPOLAR DISORDER

Crystal T. Clark, MD[1,2], Autumn M. Klein, MD[3,4], Katherine L. Wisner, MD, MS[4,5]

[1]VA Pittsburgh Healthcare System, Pittsburgh, PA, [2]Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh Department of Neurology, Pittsburgh, PA, [4]University of Pittsburgh Department of Obstetrics, Gynecology, and Reproductive Science, Pittsburgh, PA, [5]Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, PA

**Objective:** Most of the data on the use of lamotrigine (LTG) in pregnancy comes from the epilepsy literature. There is limited data on its use in pregnant women with bipolar disorder. We present new data on the serum levels (total) of LTG in pregnant patients using monotherapy for bipolar disorder and review the current evidence.

**Methods:** LTG serum samples were obtained from four Caucasian mother-infant pairs at different time points during pregnancy and postpartum.

**Results:** Case 1 – The maternal serum level-to-dose (L/D) ratios at 30 and 36 weeks, were 41% and 67% of maternal nonpregnant levels at 4 weeks postpartum, respectively. The serum level of LTG increased 59% between 30 weeks gestation and 4 weeks postpartum. The nursing infant LTG concentration was 46% of the maternal serum concentration at 4 weeks postpartum. No adverse events for the infant were reported. Case 2 - The maternal serum L/D ratios at 20, 30, and 36 weeks were 15%, 22%, and 27% of the maternal levels at 6.5 months postpartum, respectively. Postpartum, the LTG serum concentration increased five-fold between 2 weeks and 4 weeks postpartum. The infant was hospitalized 2 days after delivery for jaundice and dehydration. No subsequent adverse events were reported. The nursing infant LTG concentration was 18% of the maternal serum concentration at 4 weeks postpartum. Case 3 - Serum levels of the mother-infant pair were essentially equivalent (maternal serum = 19.5 ng/ml and umbilical cord = 20.5) at delivery. Case 4 – The breastfed infant LTG concentration at 2 weeks postpartum was 45% of the maternal serum level.

**Conclusion:** Consistent with the current literature these cases of bipolar disorder and lamotrigine treatment in pregnancy further support the prior evidence that: 1) LTG levels decrease in pregnancy then quickly and considerably increase postpartum; 2) maternal and umbilical cord serum levels are essentially equivalent at birth; 3) a decreased proportion of LTG is transferred from the mother's breast milk to the infant in comparison to that transferred during pregnancy. Adverse events in newborns exposed to lamotrigine have rarely been reported but continue to be explored. Ultimately, changes in LTG concentration in pregnancy and postpartum have implications for dosing LTG during pregnancy, postpartum, and lactation.

**Learning Objectives:**

- Lamotrigine serum levels decrease in pregnancy
- Lamotrigine serum levels increase in 2-4 weeks postpartum
- Maternal transfer of lamotrigine to the fetus is approximately 1:1
- Lamotrigine transfer through breastmilk is variable and less than that transferred to the fetus in pregnancy

**Source Of Funding:** NIMH

**Literature References:**

- Pennell, PB, et al. The impact of pregnancy and childbirth on the metabolism of lamotrigine. Neurology 2004; 62: 292-295.
- De Haan, G-J, et al. Gestation-induced changes in lamotrigine pharmacokinetics: A monotherapy study. Neurology 2004; 63:571-573.
- Liporace, J, et al. Concern regarding lamotrigine and breast-feeding. Epilepsy and Behavior 5 2004; 102-105.
- Kacirova, I et al. Serum levels of lamotrigine during delivery in mothers and their infants. Epilepsy Research 2010; 91: 161-165.

**POSTER SESSION 2**
**12:30 P.M. - 2:15 P.M.**

## COGNITIVE-BEHAVIORAL THERAPY IN WOMEN DISCONTINUING ANTIDEPRESSANT IN ANTICIPATION OF PREGNANCY

Christina Psaros, PhD[1], Marlene P. Freeman, MD[2], Steven A. Safren, PhD[1], Maria M Barsky, BS[2], Lee S. Cohen, MD[2]

[1]Massachusetts General Hospital, Behavioral Medicine Service, Boston, MA, [2]Massachusetts General Hospital, Center for Women's Mental Health, Boston, MA

**Background:** Many women are motivated to discontinue AD when trying to conceive, though the risk of depressive relapse among women who discontinue maintenance antidepressant (AD) treatment for pregnancy is high. The goal of this study was to adapt a cognitive behavioral therapy prevention of recurrence treatment (CBT-PR) for women with a history of recurrent major depressive disorder (MDD) who planned to discontinue maintenance AD treatment with the intent to conceive.

**Methods:** An open pilot study of CBT-PR was conducted in women planning or in the first trimester of pregnancy. Subjects were eligible if they 1) had a history of MDD 2) were euthymic at presentation and with a remission for at least six months 3) on maintenance AD treatment 4) independently decided to discontinue AD for pregnancy prior to study entry. Subjects received 12 weekly sessions of CBT-PR during the acute phase of the trial. Following the acute phase, subjects who had not experienced a relapse continued in a maintenance phase that included optional monthly booster sessions for up to 9 months. After baseline assessment, subjects were assessed bi-weekly by an independent rater during the acute phase and bi-monthly during the maintenance phase. Recurrence was defined as meeting criteria for MDD using the mood module of the Mini-International Neuropsychiatric Interview (MINI) or reintroduction of AD therapy; depression severity was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS).

**Results:** Twelve (N=12) subjects (mean age = 34 years, SD=3.96) with a median of 3 past episodes of major depression (range 1-15) and a median of 1 failed attempt at AD discontinuation (range 0-3) were enrolled. The mean MADRS score at baseline for the entire sample at baseline was 5.72 (SD=4.8). Average length of AD taper was 4.3 weeks (SD=2.53; range 1-9 weeks); taper schedules were determined by the subject and study psychiatrist based on what was clinically appropriate for the medication. To date, all subjects who have completed the acute phase, and those who have remained in remission have received up to four booster sessions over an additional 12 weeks. During the acute phase, two subjects experienced a relapse of major depression and an additional subject restarted AD without meeting full criteria for a major depressive episode. No subjects relapsed during the booster phase through 24 weeks. The mean MADRS score at baseline for the relapse group was 9.67 (SD=8.08) and 4.78 (SD= 2.64) for the non-relapse group. Subjects who relapsed had a mean MADRS score of 15.33 (SD=1.15) at the time of relapse; subjects who remained euthymic up to 24 weeks had a mean MADRS score of 8.33 (SD=5.61) at the end of the acute phase, and 6.33 (SD=5.9) at 24 weeks.

**Discussion:** CBT-PR appears to provide protection for some women with recurrent depression on AD therapy who discontinue their medication while trying to conceive. The extent to which euthymia is sustainable after treatment with CBT-PR in this population is an area of needed study, the results of which may broaden treatment choices for women during this crucial time.

**Learning Objectives:**

- Describe results of a pilot trial of CBT-PR among women with a history of recurrent MDD who planned to discontinue maintenance AD treatment with intent to conceive
- With further study, identify the role of CBT-PR or other non-pharmacologic interventions as potential treatment options for women who wish to discontinue AD to conceive

**Source Of Funding:** Program Funds

**Literature References:**

- Cohen L, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006;295:499-507.
- Fava G, et al.Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. Arch Gen Psychiatry. 1998 ;55:816-820.

## PREGNANCY OUTCOMES AMONG WOMEN USING ANTIPSYCHOTIC DRUGS

Simone N. Vigod, MD, MS[1,2], Joel G. Ray, MD, MS[2,3], Tara Gomes, MS[2], Valerie H. Taylor, MD, PhD[1]

[1]Women's College Hospital and University of Toronto, Toronto, Ontario, Canada, [2]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, [3]St. Michael's Hospital and University of Toronto, Toronto, Ontario, Canada

Women of childbearing age are susceptible to serious mental illness. This vulnerability is particularly pronounced during pregnancy. As such, a significant proportion of women with serious mental illness face decisions about whether or not to use antipsychotic medication in pregnancy. In fact, the Motherisk Program, a Canadian teratology information service (affiliated with the North American Organization – OTIS, the Organization of Teratology Information Specialists) reports that referrals about the use of antipsychotic medications in pregnancy increased by 170% between 1989 & 2001. Unfortunately, real-life decisions about antipsychotic medication use in pregnancy are complex and, often, poorly informed: If a woman discontinues her antipsychotic medication during pregnancy she may be at risk of relapse or worsening of her mental health condition. Nevertheless, much uncertainty remains about the fetal safety of antipsychotic drugs. This is especially true for the newer atypical antipsychotics because drug-induced changes in maternal metabolic function may have profound consequences for maternal and neonatal health. We urgently require information specific to the impact of antipsychotic drug use in pregnancy to better guide decision-making.

The aim of this proposal is to rapidly generate valid estimates of the association between antipsychotic medication use in pregnancy and the risk of adverse obstetrical and neonatal outcomes. Among women prescribed an antipsychotic drug during pregnancy, our specific study goals are to: 1. Describe obstetrical and neonatal outcomes, with comparison to 2 control groups: a) selective serotonin reuptake inhibitor (SSRI) users (active comparison group) and b) those neither prescribed an antipsychotic medication nor an SSRI during pregnancy (passive comparison group). 2. Explore whether obstetrical and neonatal outcomes seen with antipsychotic drug exposure in pregnancy differ according to psychiatric diagnosis. To achieve these goals we will use comprehensive and validated population-based Canadian linked administrative health data from the Province of Ontario (population ~ 13 million). Our data sources allow us to measure exposure to a psychotropic medication, psychiatric diagnosis & outcomes (obstetrical and neonatal). We will use a retrospective, propensity-score matched cohort study design to compare obstetrical and perinatal outcomes among women who use an antipsychotic drug in pregnancy to women not exposed to an antipsychotic medication, accounting for key prognostic factors and minimizing selection bias.

This proposed study will generate data needed for us to begin to contribute to the development of clear recommendations to better inform women and their health care providers about whether to initiate (or continue) an antipsychotic drug in pregnancy. If little harm to pregnancy or the fetus is shown, then that provides reassuring data. If harm is shown, then the emerging data may guide the type, dose & timing of use of an antipsychotic medication, or the initiation of another therapy (e.g., dietary counselling) or special surveillance (e.g., a greater number of fetal ultrasounds to assess intrauterine fetal growth). To the best of our knowledge, this will be the largest population-based study of obstetrical and neonatal outcomes among women taking antipsychotic drugs in pregnancy. Policy-makers and clinical decision-makers will greatly benefit from such information.

**Learning Objectives:**

- To understand the rationale for studying the impact of antipsychotic use in pregnancy
- To describe a population-based study design for examining pregnancy outcomes among women using antipsychotic drugs in pregnancy

**Source Of Funding:** Schizophrenia Society of Ontario - Helen Pfohl Fund

**Literature References:**

- McKenna K, Einarson A, Levinson A, Gideon K. Significant changes in antipsychotic drug use during pregnancy. Vet Hum Toxicol. Feb 2004;46(1):44-46.
- Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophr Bull. May 2010;36(3):518-544.
- Einarson A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. J Psychiatr Pract. May 2009;15(3):183-192.
- Vigod SN, Ross LE. Epidemiology of Psychotic Symptoms during Pregnancy and Postpartum in Women with Schizophrenia. Current Women's Health Reviews. 2010;6(1):17-21.

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## Save the Date: NCDEU 2013

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