LEARNING FROM THE PAST TO ADVANCE THE FUTURE OF MENTAL HEALTH TREATMENT

POSTER ABSTRACTS

50TH ANNIVERSARY MEETING

June 14 - 17, 2010 | Boca Raton Hotel | Boca Raton, FL
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All poster presentations are copied verbatim and appear in category listing per day as outlined below:

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**Poster Number Index**

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Background: Adverse events during selective serotonin reuptake inhibitor (SSRI) treatment are frequent and may lead to premature treatment discontinuation in both clinical trials and naturalistic settings. If attrition is associated with early worsening of any specific side effects or the frequency, intensity or burden of side effects, interventions to maximize retention could be tailored to patients with these events early in the course of treatment.

Methods: Outpatient adult participants (n=265) with nonpsychotic major depressive disorder entered an eight-week trial with an SSRI. At baseline and Week 2, specific side effects were evaluated with the Systematic Assessment for Treatment Emergent Events–Systematic Inquiry, and at Week 2 the Frequency, Intensity and Burden of Side Effects Rating globally assessed side effects. Attrition was defined by leaving the study at any time after the Week 2 visit.

Results: No specific Week 2 side effect, either treatment emergent or with worsening intensity, was independently associated with attrition. Global ratings of side effect frequency, intensity or burden at Week 2 were also not associated with subsequent attrition. Change in symptom severity scores between the baseline and Week 2 visits did not differ between dropouts and completers.

Conclusions: While conventional wisdom suggests that side effects are common, appear early in treatment and are associated with treatment discontinuation, current findings suggest otherwise. Neither global ratings nor specific side effects at Week 2 were related to patient attrition during SSRI treatment. Other factors appear to contribute to patient decisions about continuing with treatment.

Source of Funding: National Institute of Mental Health (Contract N01MH90003) to University of Texas, Southwestern Medical Center at Dallas (P.I.: M.H. Trivedi). This analysis was also supported in part by a National Alliance for Research on Schizophrenia and Depression Young Investigator award (D. Warden).

Literature References:
Session I–3

Prophylactic Efficacy of Fluoxetine, Escitalopram, Sertraline and Paroxetine in Unipolar Depression: Outcome after Long-Term Follow-Up

Rushniya Khairova, M.D., Ph.D., Eric Peselow, M.D., Rohit Pawar, M.B.B.S., M.S.
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Background: Unipolar major depressive disorder is a chronic, comorbid and impairing mental disorder with high lifetime prevalence. Although acute efficacy of antidepressant treatment is well established, the relative prophylactic efficacy of the antidepressants is yet to be fully determined. Studies in naturalistic settings are important in evaluating treatment outcomes with antidepressants, since controlled clinical trials include only minority of patients present in clinical practice. This study was conducted to determine the prophylactic effectiveness of two different types of commonly used antidepressants (fluoxetine, escitalopram, sertraline and paroxetine) in unipolar major depressive disorder with long term follow-up, and to identify predictors of outcome.

Methods: Patients were successfully treated with various selective serotonin reuptake inhibitors (SSRIs) for acute depression between July 1, 1993, and January 1, 2009, over an eight to ten week course. Patients were evaluated with the Montgomery–Åsberg Depression Rating Scale (MADRS). Response was defined as at least a 50% decrease in MADRS score with a final score between nine and 14. Patients were considered remitted if they achieved a MADRS score of eight or less. All patients involved in this evaluation met DSM-IV criteria for major depression. The choice of medication was determined according to clinical judgement based on such factors as past history of previous response to medication and previous history of side effects. Predictor variables were: presence of previous depressive episodes, comorbid psychiatric conditions, including personality disorders and co-treatment with psychotherapy during the prophylaxis.

Results: During an average follow-up period of 34.46 months, 23.49% of our patients remained episode free and 76.51% of patients had a relapse of depressive episode. Interestingly, escitalopram and fluoxetine had the highest prophylactic efficacy (36% and 33.33% of the patients remained symptom free, respectively), while paroxetine and sertraline showed poorer efficacy in prevention of depressive episodes (12.8% and 21.3% of patients remained symptom free, respectively). Neither presence of co-morbid psychiatric condition nor history of previous depressive episodes was predictive of the outcome of prophylaxis (p>0.05). However, co-treatment with psychotherapy dramatically increased prophylactic efficacy of antidepressant treatment, 41.17% of patients undergoing psychotherapy remained episode free as compared to 18.09% patients who received only pharmacological treatment during the prophylaxis period (p<0.05).

Conclusions: The results of this study with its long observation period indicate that escitalopram and fluoxetine appear to have prophylactic efficacy in the treatment of unipolar depression in a naturalistic setting. A positive response to prophylaxis was associated with co-treatment with psychotherapy. Taken together these preliminary data may help in the further definition of the range of clinical utility of these widely used antidepressants in treatment and prophylaxis of unipolar depressive disorder.

Source of Funding: Department of Psychiatry, Maimonides Medical Center.

Literature References:

Session I–4

Gepirone Treatment of Generalized Anxiety Disorder (GAD)

Joseph DeVeauugh-Geis, M.D.
Duke University Medical Center, Durham, NC

Background: Gepirone was designed as an improvement on buspirone and studies were planned for depression and anxiety. Positive studies have been reported with gepirone-extended release (ER) in major depressive disorder and mixed anxiety-depression. Studies of gepirone treatment of generalized anxiety disorder (GAD) have not been reported.

Methods: This was a European, double-blind, randomized, placebo-controlled, parallel group, multicenter comparison of the safety and efficacy of gepirone-immediate release (IR) and bromazepam in the treatment of moderately to severely anxious outpatients meeting modified DSM-III-R criteria for GAD. Approximately 225 patients were to be randomized to six weeks of double-blind treatment with 1–6 capsules per day (5–30 mg gepirone, 1.5–9.0 mg bromazepam or placebo). Efficacy and safety were assessed at Weeks 1, 2, 4 and 6. The primary efficacy outcome was the change from baseline on the Hamilton Anxiety Rating Scale (HAMA).

Results: There were 212 patients included in the intent-to-treat population. The three treatment groups were similar: mean age of 40 years, predominantly female and all Caucasian. The mean modal dose was 14.7 mg/day for gepirone-IR and 4.9 mg/day for bromazepam. On HAMA, mean change from baseline at endpoint, gepirone-IR (n=72) scored -17.09±9.06 (p=0.0039), while bromazepam (n=72) scored -15.71±8.89 (p=0.038), compared to placebo (n=68) -12.2±10.88. On the HAMA subscales, both gepirone (p=0.017) and bromazepam (p=0.034) were better than placebo on the psychic subscale, but only gepirone (p=0.004) was better than placebo on the somatic subscale. The most common adverse events were dizziness, insomnia and nausea for gepirone; and drowsiness for bromazepam.

Conclusions: In this population, gepirone-IR, was statistically significantly better than placebo and comparable to or better than the benzodiazepine, bromazepam. Studies of gepirone-ER for treatment of GAD are planned.

Source of Funding: Bristol-Myers Squibb Company. This analysis and report supported by Fabre-Kramer Pharmaceuticals, Inc.

Literature References:
Session I–5

The Mediation of Depression between Subjective Burden and Positive Aspects of Caring, and the Role of Antidepressants in Family Caregivers of Alzheimer’s Disease

Joanne DeVeacha-Gleiss, Ph.D.¹, Sylvia Bigatti, Ph.D.²

¹Walden University, Chapel Hill, NC; ²Indiana University School of Medicine, Indianapolis

Background: The care provided by family members of patients with Alzheimer’s disease (AD) can lead to role strain and personal strain, which lead to burden. While caregiver research has found that burden often leads to depression, the literature rarely discerns between the impact of objective (the tasks) versus subjective (the feelings) burden. There is also a lack of information on medication use for caregivers who are depressed. Additionally, depression is the end point of most of these studies. A factor that may predict whether the experience of caregiving is viewed positively or not.

Methods: Baseline data from 637 dyads (caregivers and care-recipients) from the Resources to Enhance Alzheimer Caregiver Health (REACH II) study were analyzed. Multiple regression analyses were used to assess the potential mediator effects of depression (Center for Epidemiology Scale–Depression [CES-D]) on subjective burden (Zarit Burden Interview), objective burden (Activities of Daily Living/Instrumental Activities of Daily Living) and the Positive Aspects of Caring Scale. Univariate analyses were used to evaluate potential moderator effects of antidepressant use on depression. Multiple regression analyses also explored subjective burden predictors of depression.

Results: Depression was found to significantly mediate the relationship between subjective burden and positive aspects of caring. The moderating effect of antidepressants was not significant. However, among caregivers not taking antidepressant medication, those who scored in the depressed range on the CES-D had a 9% lower score on positive aspects of caring than medicated caregivers who were not depressed. Depression was predicted by several subjective burden items, including role strains related to work and relations with the patient, loss of health and control over one’s life and feeling that one should do more.

Conclusions: Caregivers who experienced higher levels of subjective burden found the experience to be less positive. The impact of subjective burden on the ability of caregivers to identify positive aspects of caregiving is dependent on their level of depression. Furthermore, antidepressants may be serving as a buffer to some of the stresses of caregiving. Combined, these findings suggest the need to identify depressed caregivers and consider medication treatment as an option for their care. Suggestions for future research and clinical implications of this research are discussed.

Source of Funding: National Institute on Aging (AG13265).

Literature References:

Session I–6

Identifying Trajectories of Antipsychotic Treatment Response in Patients with Schizophrenia

Michael G. Case, M.S.¹, Virginia L. Stauffer, Pharm.D.¹, Haya Ascher-Svanum, Ph.D.², Robert Conley, M.D.¹, Shirit Kapur, M.D.¹, John M. Kane, M.D.¹, Sara Kollack-Walker, Ph.D.¹, Jayanthi Jacob, Ph.D.¹, Bruce J. Kinon, M.D.¹

¹Lilly USA, LLC, Indianapolis, IN; ²Eli Lilly and Company, Indianapolis, IN; ³King’s College of London, UK; ⁴The Zucker Hillside Hospital, Glen Oaks, NY

Background: Schizophrenia is a heterogeneous disorder in terms of response to antipsychotic treatment. Many studies find that about 70% of patients fail to experience at least minimal response early in the treatment. Recent research to identify early responders/non-responders to treatment have commonly used two a priori cut off measures: the degree of categorical symptom improvement and the duration of treatment.¹ To account for late responders and unsustained response patients misclassified in the dichotomous grouping, an alternative method of treatment response follow-up was explored.

Methods: Growth mixture modeling (GMM) was explored as an alternative method to classify clinical progression patterns. The GMM was fit into the general latent variable framework of the Mplus program.² GMM was applied to data from a randomized, double-blind, 12-week study consisting of 628 patients with schizophrenia or schizoaffective disorder treated with risperidone or olanzapine. To identify the appropriate number of response trajectories, the Bayesian Information Criterion (BIC) was used.

Results: Based on the Positive and Negative Symptom Scale (PANSS) total score over a 12-week period incorporating outcome at all time points, naturally occurring homogenous trajectories from varying individual responses were identified. Good statistical fit was achieved with two-piece growth mixture models with the first four visits until Week 3 modeled quadratically and the remaining four visits over nine weeks modeled linearly. Comparison of models with different number of classes revealed a four class model with new insight into the heterogeneity of antipsychotic response. A unique class of responders with rapid improvement in illness symptoms was identified along with three other classes of patients representing non-responders, gradual responders, and unsustained responders to treatment.

Conclusions: Growth mixture modeling is a useful framework when observations are collected over time with a fundamental heterogeneity in the population studied. Identification of naturally embedded groups of responders/non-responders to treatment may find application in translational research such as pharmacogenetics or tailored therapeutics.

Source of Funding: Lilly USA, LLC, a subsidiary of Eli Lilly and Company.

Literature References:
Efficacy of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy in Patients with Major Depressive Disorder (MDD): Pooled Analysis of Data for Patients with Different Levels of Baseline Disease Severity

Michael Thase, M.D.¹, Stuart Montgomery, M.D.¹, George Papakostas, M.D.¹, Michael Bauer, M.D.², Madhukar Trivedi, M.D.², Henrik Svedsater, Ph.D.², Urbain Gustafsson, Ph.D.², Hans Eriksson, M.D., Ph.D., M.B.A.³

¹University of Pennsylvania, Philadelphia, ²Imperial College School of Medicine, London, UK, ³Massachusetts General Hospital, Boston, ⁴University Hospital Carl Gustav Carus, Dresden, Germany, ⁵University of Texas, Southwest Medical Center, Dallas, ⁶AstraZeneca R&D, Mölndal, Sweden, ⁷AstraZeneca Research and Development, Soderfjärne, Sweden

Background: Major depressive disorder (MDD) is a debilitating disorder which poses a significant healthcare problem. Patients with severe depression are at greater risk of complications, such as treatment resistance and increased functional impairment, compared with patients with less severe depression. The effects of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with MDD were evaluated for different levels of disease severity.

Methods: Pooled data from four acute (quetiapine XR 50, 150 and 300 mg/day doses combined) six- or eight-week placebo-controlled quetiapine XR monotherapy studies (D1448C00001, D1448C00002, D1448C00003 and D1448C00004) were analyzed. Key inclusion criterion for all studies was a Hamilton Rating Scale for Depression (HAM-D) total score ≥22 at baseline. Primary endpoint was change from randomization to study end in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. A post hoc analysis in six severity cohorts (defined by a MADRS total score at randomization of ≥24, ≥26, ≥28, ≥30, ≥32 or ≥34) assessed change from randomization in MADRS total score and MADRS response (≥50% reduction in MADRS total score) at endpoint (Week 6 or Week 8).

Results: In total, 1,752 patients (the ‘all patients’ group) were assessed (MADRS ≥24 at randomization, n=1601; ≥26, n=1467; ≥28, n=1269; ≥30, n=1038; ≥32, n=745; ≥34, n=500). At endpoint, quetiapine XR significantly reduced mean MADRS total score (p-values for L5 mean versus placebo) in ‘all patients’ (effect size 0.30; p<0.001 versus placebo) and in all six severity cohorts ≥24, ≥26, ≥28, ≥30, ≥32 (effect size: 0.31, 0.32, 0.32, 0.30, 0.29, respectively; all p<0.001 versus placebo), and ≥34 (effect size: 0.26; p<0.01 versus placebo). In the quetiapine XR group, MADRS response rates were significantly higher versus placebo in the ‘all patients’ group (52.5% versus 40.9%; p<0.001) and in all six severity cohorts ≥24 (52.0% versus 40.7%; p<0.001), ≥26 (52.7% versus 40.9%; p<0.001), ≥28 (52.3% versus 39.6%; p<0.001), ≥30 (51.8% versus 39.6%; p<0.001), ≥32 (49.4% versus 36.5%; p<0.001) and ≥34 (48.6% versus 36.3%; p<0.001) at endpoint. Safety and tolerability results were consistent with the known tolerability profile of quetiapine.

Conclusions: In patients with MDD, quetiapine XR monotherapy significantly improved depressive symptoms versus placebo irrespective of baseline disease severity, including patients with severe levels of depression.

Source of Funding: AstraZeneca.

Literature References:

Session I–8

Applying Discrete Choice Experiments in Mental Health—An Example on Parents’ Preferences in Attention Deficit Hyperactivity Disorder (ADHD) Treatment

Jörg M. Fegert, M.D.¹, Lara Slawik², Matthias Nübling, Ph.D.³, Axel Mühlbacher, Ph.D., M.Sc.⁴

¹University Hospital Ulm, Germany, ²Janssen-Cilag GmbH, Neuss, Germany, ³GEB mbH: Empirical Consulting, Denzlingen, Germany, ⁴IGM Institut Gesundheitsökonomie und Medizinmanagement, Neubrandenburg, Germany

Objectives: While assessing and allocating treatment options for children with attention deficit hyperactivity disorder (ADHD), health care providers should take the parents’ preferences into account since the parents’ acceptance and support is crucial for treatment success. Discrete choice experiments (DCE) are increasingly applied in the health sector to elicit the participants’ (e.g., patients’, insured persons’, caregivers’) preferences for health care programs and products (i.e., to weigh the importance these persons attribute to treatment characteristics). The applicability of DCEs in mental health and in particular with primary caregivers in ADHD is investigated in this study.

Methods: Relevant characteristics of an “ideal” medical ADHD treatment from the parents’ perspective were collected by a literature review and a qualitative study with focus groups in order to achieve content validity. In the subsequent quantitative study, preferences for an ADHD treatment were investigated by using direct measurement (23 aspects, Likert-scale) and a DCE (eight pairs of treatment options, six dichotomous characteristics). Preferences were analysed with multivariate procedures (factor analysis, probit/ logit models).

Results: Questionnaires were completed by 121 primary care givers (101 mothers, 16 fathers, four others) on behalf of their school age child (six to 14 years, 87% male). All characteristics were statistically significant in the DCE. Highest relative importance was attributed to an improvement in the child’s social situation and its emotional state (38% and 21%). Another essential characteristic was a long-lasting drug effect (18%), whereas side effects (8%), dosing flexibility (7%) and discretion (8%) were assessed as less important.

Limitations: Preferences reflect cultural attitudes and might not be completely generalizable to other contexts. Participants were clinically referred patients and not a population-based sample.

Conclusions: The presented study demonstrates feasibility of methods applied to caregivers (parents) of children with ADHD in order to systematically assess treatment preferences. This work may eventually lead to improved ADHD treatment and a more efficient resource allocation in mental health care.

Source of Funding: Janssen Cilag.

Literature References:
Session I–9

Antidepressant-Placebo Differences over an Eleven Year Period in a Sample of Patients with High and Similar Baseline Scores

Arif Khan, M.D.1, Amritha Bhat, M.D.1, James Faucett, M.S., M.A.1, Russell Kolts, Ph.D.1, Walter Brown, M.D.2

1Northwest Clinical Research Center, Bellevue, WA, 2Eastern Washington University, Cheney, 3Brown Alpert Medical School, Providence, RI

Background: Randomized placebo controlled antidepressant clinical trial drug-placebo difference scores have steadily declined the past three decades.1 During this same time period a decrease in patient severity of symptoms at baseline has occurred.2 The current study was designed to examine anti-depressant-placebo difference scores over an 11-year period in a sample of depressed patients with high and similar baseline scores.

Methods: We analyzed data from a total of 472 patients who participated in 16 unblinded trials at the Northwest Clinical Research Center, Bellevue, WA, between 1995 and 2006. Randomization codes were obtained from study sponsors for 301 patients assigned to antidepressants and 172 patients assigned to placebo. Mean baseline Hamilton Rating Scale for Depression–17 item (HAMD-17) scores and mean antidepressant-placebo difference scores were calculated for each study. Correlations examined relationships between year of conduct of the trial and mean baseline HAMD-17 score, and year of conduct of the trial and mean antidepressant-placebo difference.

Results: There was no significant correlation between baseline HAMD score (M=25.88, SD=1.95) and year of conduct of trial (r=0.13, n=16, p=0.65), and there was no significant correlation between antidepressant-placebo difference (M=3.42, SD=4.1) and year of conduct of trial and (r=-0.20, n=14, p=0.49). Baseline severity of depression and drug-placebo difference scores did not reduce over an eleven year period in this sample of patients with stable baseline scores from a single center.

Conclusions: These data suggest that for depressed patients with sufficiently severe symptoms at baseline, the magnitude of change with placebo and antidepressant-placebo differences remain stable, regardless of when they were recruited.

Source of Funding: Northwest Clinical Research Center.

Literature References:

Session I–10

Psychometric Properties of the Wender-Reimherr Adult Attention Deficit Disorder Scale

Fred Reimherr, M.D.1, Barrie K. Marchant, M.S.1, Reid J. Robison, M.D.1, Diane Robison, Ph.D.2, Paul Wender, M.D.2, Erika Williams, M.S.W.3, Corinne Halls, M.S.1, Douglas Kondo, M.D.1

1University of Utah, Salt Lake City, 2Harvard University, Andover, MA

Background: The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) is a clinician rated scale for assessing adult attention deficit hyperactivity disorder (ADHD) based on the Utah Criteria.1 It assesses seven symptom areas: attention difficulties, hyperactivity/restlessness, temper, affective lability, emotional over-reactivity and disorganization) are either associated features or not included. Their inclusion makes the WRAADDS unique from DSM-based scales. While it has proven effective in clinical trials, the lack of published psychometric information has limited its use. This report documents both reliability and validity for the WRAADDS.

Methods: The normative sample consisted of 120 males and females ages 20 through 49 inclusive. Exclusion criteria included known personal or family history of ADHD, personal history of an Axis I disorder in the last three months and any history of hospitalization or treatment for a psychotic disorder. The ADHD subjects were taken from clinical trials of adult ADHD: (1) two identical clinical trials of atomoxetine; (2) a clinical trial of OROS-MPH; and (3) a clinical trial of Methylphenidate Transdermal System.

Results: Test-retest using 51 adult ADHD subjects from two studies was excellent (r=0.96). Inter-rater reliability using 67 adult ADHD subjects from two studies was excellent (r=0.75). Internal consistency was acceptable (Cronbach’s alpha =0.78). Removal of any of the seven subscales resulted in only a small decrease in internal consistency. Concurrent validity was assessed using the Conners’ Adult ADHD Rating Scales (CAARS).2 The total WRAADDS was significantly correlated with the Total CAARS (r=0.50, df=534, p<0.001). The hyperactivity + impulsivity subscales of the WRAADDS correlated with the hyperactivity/impulsivity subscale of the CAARS (r=0.601, df=534, p<0.001). The attention + disorganization subscales of the WRAADDS correlated with the inattention subscale of the CAARS (r=0.430, df=534, p<0.001). Discriminate validity was evaluated by distinguishing between adults with and without ADHD (matched for age, sex and race). There was a significant difference between the normative and ADHD subjects for the total WRAADDS (F1,228=1075.6, p<0.001) and each of the seven symptom areas (p<0.001).

Conclusions: The WRAADDS assesses a more comprehensive set of adult ADHD symptoms than DSM-IV based scales. These data indicate that it has adequate reliability and validity for continued use in research and treatment of adult ADHD.

Source of Funding: In part by an unrestricted educational grant from Eli Lilly, and Company.

Literature References:
A Randomized, Controlled Clinical Trial Assessing the Effect of Guanfacine Hydrochloride on QT/QTc Interval in Healthy Adults

Lawrence Satin, M.D., F.A.C.C.1, Patrick Martin, M.D.2, Gerald Tremblay, M.D., J.D.3, Jaideep Purkayastha1

1CardioCore, Bethesda, MD, 2Shire Development Inc., Wayne, PA

Background: Guanfacine extended release (GX R; Intuniv®), Shire U.S. Inc.) is approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged six to 17 years. A thorough QT interval study of guanfacine was performed to appropriately assess the impact of guanfacine on the QT interval.

Methods: This double-blind, three-period, crossover study randomized 83 healthy adults to one of six sequences of immediate-release guanfacine hydrochloride (HCl) at therapeutic (4 mg) and supratherapeutic (8 mg) doses, placebo and moxifloxacin HCl (positive control). Continuous 12-lead electrocardiograms were extracted and plasma concentrations of guanfacine were assessed predose and 1, 2, 3, 4, 5, 6, 8 and 12 hours postdose. QT intervals were corrected with both a subject-specific method (QTcNi), that is preferred for medications that impact QT interval prolongation and proarrhythmic potential for non-cardiac disease receiving stimulant (ADHD) treatment. Despite their efficacy and long history of use, recent concerns exist regarding their potential adverse cardiovascular (CV) effects.1,2 The nature and magnitude of these effects is controversial. This data review evaluates a decade’s worth of published reports in the context of stimulant treatment of ADHD and the risk of CV events.

Methods: All placebo-controlled and open-label extension trials published after 2000 reporting heart rate (HR), blood pressure (BP) and/or QT interval data in children, adolescents or adults with ADHD treated with methylphenidate (MPH) or mixed amphetamine salts (MAS) were included. CV data from all treated subjects were compared across studies.

Results: Three placebo-controlled trials evaluated therapeutic MAS (three to six weeks treatment; N=659); one reported significant increases from baseline in mean HR (5.0 bpm; p<0.05); none noted significant BP or QT interval changes. Four open-label extension trials evaluated MAS (15 wks–2 yrs; N=3087); all reported significant increases in HR (1.5 to 4.4 bpm; p<0.001) and systolic BP (0.6 to 3.5 mm Hg; p<0.05 or p<0.001), and three noted QT interval increases (2.7-7.2 ms; p<0.05). Three placebo-controlled trials evaluated MPH treatment (4–6 wks; N=253); two trials reported significant HR increases (4.5 and 7.0 bpm; p<0.001), and one reported increases in systolic BP (1.5 mm Hg; p<0.05), diastolic BP (4.0 mm Hg; p<0.001), and QT interval (7.0 ms; p<0.05). One of two MPH open-label extension trials (6 mo–1 yr; N=602) observed significant increases in HR (3.9 bpm; p<0.001), systolic BP (3.3 mm Hg; p<0.001) and diastolic BP (1.5 mm Hg; p<0.001). No deaths or hospitalizations due to CV adverse events were reported in any of the studies.

Conclusions: Therapeutic use of stimulants for the treatment of ADHD can increase HR, BP and QT interval. Although the magnitude of these effects appear small, we recognize both a potential for acute consequences in children with pre-existing cardiac disease and uncertainties regarding sequelae of long-term exposure to these small effects in all children. Screening for occult disease with a baseline electrocardiogram (ECG) is reasonable to consider for all patients starting stimulants.

Source of Funding: Novartis Pharmaceuticals Corporation.

Literature References:
Effects of Stimulants on the Cerebellar Morphology in Attention Deficit Hyperactivity Disorder (ADHD)

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Background: Neuroimaging research of attention deficit hyperactivity disorder (ADHD) has consistently demonstrated brain abnormalities in youth with ADHD with most prominent differences documented in the cerebellum. The fact that the developmental trajectories for the cerebellum remain parallel for both patients and controls suggests that both genetic and environmental influences in ADHD are fixed and independent of medication treatment. More specifically, decreased volume of the superior cerebellar vermis appears to represent an important substrate of these non-progressive anatomical changes that underlie ADHD whereas the cerebellar hemispheres are more plastic, state-specific markers that may potentially constitute targets for biological interventions. Therefore, implementation of neuroimaging techniques that can differentiate between cerebellar substructures may provide useful additional information about the effect of biological treatments on regional cerebellar morphology.

Objective: To evaluate the effect of stimulant treatment on the cerebellar morphology in youth with ADHD with the use of surface morphometry. Based on previous reports it is hypothesized that children with ADHD who received naturalistic stimulant treatment will exhibit larger regional volumes in the cerebellar hemispheres when compared to untreated counterparts.

Methods: We compared 42 children and adolescents with ADHD and 57 control ages eight to 18 years, in a cross-sectional, case-control study design with measures of surface morphology of the cerebellum used as main outcome measures. Of the ADHD group 31 children have received naturalistic treatment with stimulant agents from minimum of three to maximum of 108 months (Mean = 43.3, SD + 29.1).

Results: Surface maps showed significantly decreased regional volumes of the anterior-lateral surfaces of the cerebellar hemispheres bilaterally (p<0.0001) in individuals with ADHD versus controls. Conversely, youth with ADHD who received stimulant treatment exhibited significantly larger volumes in these same areas compared to untreated counterparts.

Conclusions: These results confirm previous findings demonstrating reduced hemisphere regional volumes of the cerebellum in youth with ADHD compared to controls. They also provide preliminary data indicating that these same areas are relatively enlarged in treated versus untreated patients with ADHD.

Source of Funding: National Institute on Drug Abuse/American Association for Child and Adolescent Psychiatry (K23 PA-00-003); National Institute of Mental Health (MH068318, MH59139).

Literature References:
Session I–15

A Study of the Coadministration of Guanfacine Extended Release and a Psychostimulant for the Treatment of Attention Deficit Hyperactivity Disorder: Design and Rationale

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Background: Increasingly, children and adolescents with attention deficit hyperactivity disorder (ADHD) are given combined medication regimens for refractory or comorbid ADHD. Despite this, few controlled studies are available on the concomitant use of two medications for ADHD. One such combination of interest is the coadministration of α2-adrenoceptor agonists and psychostimulants. Currently, α2-adrenoceptor agonists are often administered nightly, whereas little data exist on differences in efficacy and tolerability of daytime versus nighttime administration. We describe a controlled study of a recently approved extended-release preparation of guanfacine (GXR), a selective α2-adrenoceptor agonist, added to a stable psychostimulant regimen for the treatment of ADHD in subjects with suboptimal response to the psychostimulant.

Methods: Pediatric and adolescent subjects aged six to 17 years with a DSM-IV-TR diagnosis of ADHD confirmed by structured interview were eligible to participate. Subjects were required to have an ADHD Rating Scale Version IV (ADHD-RS-IV) score of ≥24 at baseline, and be on a stable, once-daily dose of a long-acting psychostimulant (amphetamine or methylphenidate) for 24 weeks with suboptimal response in the opinion of the investigator. Subjects were randomized (1:1:1) to receive their baseline psychostimulant regimen in addition to placebo, GXR dosed in the morning, or GXR dosed in the evening. Guanfacine was increased in 1-mg weekly increments up to a maximum optimal dose of 4 mg/d. The five-week dose-optimization phase was followed by a three-week dose-maintenance phase. ADHD outcome was assessed weekly using the ADHD-RS-IV (the primary efficacy measure). Secondary efficacy measures included the Clinical Global Impressions–Improvement Scale, the Clinical Global Impressions–Severity of Illness Scale, the Conners’ Global Index–Parent (assessing symptoms in the morning and in the evening separately), the Parent’s Global Assessment, the oppositional subscale of the Conners’ Parent Rating Scale–Revised Long Form, and the Wil-Hammer Before School Function Score. Safety parameters were assessed with the Post-Sleep Questionnaire. Safety was assessed through vital signs, reports of adverse events, electrocardiograms, physical examination and laboratory monitoring.

Results: Of the 615 subjects who were screened, 461 were randomized. There were 59 enrolling sites. Enrollment lasted approximately 65 weeks.

Conclusions: The current study demonstrates an approach to addressing suboptimal response to the psychostimulant. The complexity of such multisite studies, the current study has demonstrated the feasibility of combined medication trials for design and recruitment. Given the complexity of ADHD and the need for controlled studies of combined treatments, well-conducted studies are essential to inform the field.

Source of Funding: Shire Development Inc.

Literature References:

Session I–16

Pioglitazone for the Treatment of Bipolar Depression and Co-Occurring Insulin Resistance: Preliminary Evidence for Insulin Sensitization as a Novel Mechanism of Antidepressant Action

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Background: Approximately one-third to one-half of patients with bipolar disorder meet criteria for insulin resistance. Often identified by abdominal obesity and other parameters of the metabolic syndrome, insulin resistance has been identified as a risk factor for the development of depression and is associated with greater psychiatric symptom severity. Emerging evidence also indicates that insulin and insulin-signaling pathways play a prominent role in regulating catecholamine transporters and dopamine neurotransmission. Pioglitazone is a potent insulin-sensitizer that has been found to have neuroprotective and anti-inflammatory effects that may be beneficial in treating mood symptoms. For these reasons, we hypothesized that in patients with acute bipolar depression and co-occurring insulin resistance, pioglitazone treatment would result in decreased depressive symptom severity and an improvement in insulin sensitivity.

Methods: A total of 15 patients with bipolar I or II disorder and co-occurring insulin resistance received open-label pioglitazone 15–30 mg daily for eight weeks. Bipolar disorder was confirmed by the Mini-International Neuropsychiatric Interview and insulin resistance was confirmed by the presence of metabolic syndrome or meeting two of the following four criteria: (a) body mass index ≥28, (b) fasting triglycerides ≥150 mg/dL, (c) fasting glucose ≥100 mg/dL, (d) Triglyceride/HDL-cholesterol ratio ≥3.0. Pioglitazone was added adjunctively to ongoing treatment with a mood stabilizer. No other antidepressant or mood stabilizer was added during the study or a minimum of four weeks prior to enrollment.

Results: Over eight weeks of treatment, pioglitazone was associated with a significant reduction in depressive symptom severity as measured by the Inventory of Depressive Symptoms (IDS-C) total score (-2.07 ± 1.33; p<0.001) and self-reported Quick Inventory of Depressive Symptoms (QIDS-SR) total score (-8.1 ± 4.4; p<0.001). Response (≥50% reduction in IDS-C total score) was achieved by 60% (N=9) of patients and remission (IDS-C total score ≤12) by 20% (N=3) of patients. Insulin resistance was significantly reduced as assessed by the HDL-cholesterol/triglyceride ratio (-1.0 ± 1.3; p=0.02). Fasting glucose levels also decreased significantly (-12.5 ± 19.5; p=0.03) over eight weeks.

Conclusions: Pioglitazone treatment in patients with bipolar depression and co-occurring insulin resistance resulted in clinically significant reductions in both clinician- and patient-rated assessments of depression severity. Pioglitazone was also associated with a significant reduction in fasting glucose and in the HDL-cholesterol/triglyceride ratio, a proxy measure of insulin resistance. These preliminary findings suggest that insulin sensitizers may represent a novel treatment option for depression that co-occurs with insulin resistance or the metabolic syndrome.

Source of Funding: NARSAD, Cleveland Foundation.

Literature References:
Session I–17

Predictors of Risperidone Serum Concentration in Youths
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Background: When given alone, risperidone may be more rapidly metabolized in youths compared to adults. However, little is known about its metabolism in a clinical sample, where polypharmacy is common. Such data are important since common risperidone side effects, like hyperprolactinemia, are dose-dependent.

Methods: Seven to 17 year-old patients treated with risperidone for at least six months were recruited. Treatment with other antipsychotics, but not other psychotropics, led to exclusion as did the presence of serious medical or neurological disorders, the use of contraception, or pregnancy. Demographic and clinical variables were collected upon enrollment and the medication history was extracted from the medical record. In order to measure risperidone and 9-hydroxy-risperidone concentrations, a fasting (in 93%) serum sample was obtained, before the morning dose (in 93%).

Results: One hundred-seven participants (92% males, median age: 11.3 years, interquartile range [IQR]: 4.3) were recruited. Attention deficit hyperactivity disorder (86%) and disruptive behavior disorders (65%) were the most common diagnoses, though comorbidity was the rule. At enrollment, the median daily dose of risperidone was 0.03 mg/kg (IQR: 0.3) and the median treatment duration was 2.2 years (IQR: 2.4). The most commonly co-prescribed psychotropics included: psychostimulants (71%), selective serotonin reuptake inhibitors (50%), and α2-agonists (32%). Cytochrome CYP2D6 inhibitors were divided in three non-overlapping categories: prominent (fluoxetine, paroxetine, fluvoxamine or bupropion, 30%), intermediate (sertraline, 9%), and weak inhibitors (citalopram or escitalopram, 13%). Multiple linear regression analysis revealed that the serum levels of both risperidone and its metabolite were strongly associated with the weight-adjusted dose of risperidone and time since the last dose (all p values <0.001). In addition, risperidone concentration, but not that of its metabolite, increased with Tanner stage (p<0.04) while male sex (p<0.03) and body mass index (BMI) z score (p<0.002) predicted a higher level of only 9-hydroxy-risperidone. Finally, the use of CYP2D6 inhibitors was more strongly correlated with risperidone concentration (p<0.0001) than with its metabolites (p>0.05). The duration of risperidone treatment was not associated with either concentration. The models accounted for 55% of the variance in risperidone level, 64% of its metabolites, and 70% of the variance in their combined concentration.

Conclusions: In chronically-treated youths, the metabolism of risperidone depends on the stage of sexual development while that of 9-hydroxy-risperidone varies with sex and body fat. Moreover, CYP2D6 inhibitors more strongly affect risperidone metabolism than that of its metabolite.

Source of Funding: NARSAD, the National Center for Research Resources (RR00059) and the National Institute of Mental Health (R21MH080968 and K23MH085005).

Literature References:

Session I–18

Dimensional and Categorical Measures of Personality Pathology in the Prediction of Treatment Outcome of Depression
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Background: Depressed patients with comorbid personality pathology appear to fare worse in treatment for depression than those without this additional pathology. Current work is considering the use of dimensional approaches to the measurement of personality pathology rather than the present categorical system, particularly for the construction of DSM-V.1 A dimensional approach may be more reliable and may address the heterogeneity of personality pathology and the importance of subthreshold presentations.2 We aimed to determine the effect of dimensional and categorical measures of personality pathology on the outcome of patients receiving treatment for depression. We hypothesized that both dimensional and categorical measures of personality pathology would predict time to remission and remission status (remit versus no remit), but the dimensional measure would be a better predictor of these outcomes.

Methods: Individuals suffering from an episode of unipolar major depression (n=279) received interpersonal psychotherapy3 and pharmacotherapy for depression. Depressive symptoms were measured using the Hamilton Rating Scale for Depression–17-item (HRSD-17). The primary outcome of interest was the effect of personality pathology on time to remission and treatment outcome on monotherapy at 12 weeks. Remission was defined as a mean HRSD-17 score of seven or below over a period of three weeks during the acute phase. Personality disorders were diagnosed using the Structured Clinical Interview for DSM Disorders II (SCID-II). Personality pathology was measured dimensionally by calculating a score for each participant derived by summing the positive probes endorsed on the SCID-II.

Results: This sample included 276 moderately depressed adults. When identical covariates were entered into separate Cox proportional hazard models the presence of one or more personality disorders was not related to time to remission of depression (Exp(β) =0.831, CI=0.58–1.20, p=0.321), but those who reported a higher level of personality pathology (measured dimensionally) experienced a longer time to remission than those with a lower level of pathology (Exp(β) =0.98, CI=0.97–0.996, p=0.009). Logistic regression analysis suggest that the categorical measure of personality pathology did not predict treatment outcome (Exp(β) =0.822, CI=0.47–1.43, p=0.466), but individuals with a higher level of personality pathology (measured dimensionally) were less likely to remit from depression (Exp(β) =0.98, CI=0.96–0.997, p=0.023). The analyses also show that personality pathology did not moderate the effect of treatment assignment on time to remission or treatment outcome (all p-values ns).

Conclusions: The findings support our hypothesis that a dimensional measure of personality pathology may be more useful in determining which patients will recover faster in treatment for depression and which are more likely to remit.

Source of Funding: National Institute of Mental Health (MH65376, E. Frank, PI).

Literature References:
Session I–19

Concise Associated Symptoms Tracking (CAST) Scale and Concise Health Risk Tracking (CHRT) Scale: Brief Self and Clinician Ratings of Suicidality and Associated Symptoms

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Background: Food and Drug Administration (FDA) warnings recommend monitoring treatment emergent symptoms associated with the initiation of antidepressant medications given that they may indicate safety concerns. No brief reliable rating instruments to assess treatment emergent symptoms: irritability, anxiety, mania, panic and insomnia are available. Few, brief, reliable ratings of suicidality in adults are available. The primary objective of the Suicide Assessment Methodology Study (SAMS) was to evaluate the psychometric properties of two brief self- and clinician-rated measures that assess the antidepressant treatment emergent symptoms outlined in the FDA warnings: (1) the 17-item Concise Associated Symptom Tracking (CAST) scale, which assesses irritability, anxiety, mania, panic and insomnia; and (2) the 12-item Concise Health Risk Tracking (CHRT) scale that assesses factors related to the risk of suicide attempt or completion.

Methods: This study was a naturalistic observation of 240 adult outpatients with nonpsychotic major depressive disorder (MDD) from six primary care and nine mental health settings in the National Institute of Mental Health (NIMH)-funded Depression TGAs Network. 1 Patients were evaluated during an eight-week, open-label trial with the clinician’s choice of a selective serotonin reuptake inhibitor (SSRI). Psychometric evaluations were conducted for the patient self-report and clinician rated versions of the CAST (CAST-SR, CAST-C) and CHRT (CHRT-SR, CHRT-C).

Results: The factor analysis of the CAST-SR and CAST-C identified five primary factors. One item cross loading on two factors and when eliminated led to a 16-item solution. The Cronbach’s alpha for the 16-item version was 0.78 (CAST-SR) and 0.80 (CAST-C). The five independent factors were: (1) irritability, (2) anxiety, (3) mania, (4) panic and (5) insomnia. The factor analysis of the CHRT-SR and CHRT-C identified three primary factors. Several items cross loading on multiple factors and when eliminated led to a seven-item solution. The Cronbach’s alpha for the seven item version was 0.77 (CHRT-SR) and 0.78 (CHRT-C). The three independent factors were: (1) current suicidal thoughts and plans, (2) perceived lack of social support and (3) negative self-view.

Conclusions: The 16-item CAST has demonstrated excellent psychometric properties and could be used in monitoring antidepressant treatment emergent symptoms associated with suicidal ideation and behavior as recommended by the FDA warnings. Both the clinician-rated and self-report versions of the seven-item CHRT-C7 have excellent psychometric properties and can be used to monitor suicidal risk in clinical practice and research settings. In order to maintain consistency with current standards of reporting an additional behavioral module will be included with the CHRT-C7 in future studies.

Source of Funding: National Institute of Mental Health (N01 MH90003-01).

Literature References:


Session I–20

An Alternative Statistical Approach to Identifying Treatment-Responsive Classes in a Depression Trial

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Background: Sertraline Against Depression and Heart Disease in Congestive Heart Failure (SADHART-CHF) is a National Institute of Mental Health (NIMH)-sponsored, prospective, randomized, double-blind, placebo-controlled trial, designed to assess the safety and efficacy of sertraline in the treatment of heart failure patients with major depressive disorder. The primary outcome score of Hamilton Rating Scale for Depression (HAM-D) over 12 weeks (end of the acute trial phase) did not distinguish the sertraline and placebo groups. 1 No statistical attempt was made to determine whether one or more subgroups of patients were responsive to the drug, and if so, their characteristics. We are using generalized growth mixture models 2 to determine whether this dataset contains multiple trajectory classes. Subgroup characteristics may enable better design, and identify subjects who will most benefit from the drug.

Methods: The SADHART-CHF trial included a 12-week acute masked treatment phase, with data also gathered at Weeks 0, 2, 4, 6, 8 and 10. Of the sample of 469 subjects, 235 were randomized to sertraline and 234 to placebo.

Results: A piece-wise quadratic model best fit the data. A single class model fit the placebo group. A two class model fit the treatment group, one (better outcome class, 90% of the treatment group) consisted of a linear fit with a steep decline in HAM-D from baseline to Week 2, and a linear fit from Week 2 to Week 12, with the HAM-D declining from nine to seven (a cut-off below which is considered remission) by Week 12. The second class (poorer outcome class), consisted of 10% of the treatment sample; HAM-D was greater than 17 at Week 2 and remained at that level until Week 12. Better and poorer outcome classes were compared on baseline sociodemographic, psychiatric, other cardiac and comorbid conditions. At baseline, depression scores of Beck Depression Inventory (25 versus 19) and HAM-D (24 versus 17), and body mass index (36 versus 31) were significantly larger for the poorer outcome group. The poorer outcome group also had worse (though not significantly) cardiac events through the 12-week followup.

Discussion: In treating depression, greater attention needs to be paid to the severely depressed obese subjects with poor cardiac outcomes.

Source of Funding: Duke University’s CTSA grant UL1 RR024128-04 from NCRR/NIH. National Institutes of Health, National Institute of Mental Health grant (2P50-MH60451).

Literature References:

Session I – 21

Theta-Burst Stimulation for the Treatment of Depression: Efficacy, Safety and Mechanisms

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Medication resistant depression is a debilitating condition that has few therapeutic options. There are a few device-based therapies that have received Food and Drug Administration (FDA) approval for this indication, but they either have risks of significant side effects (e.g., electroconvulsive therapy), or are not effective for the most resistant patients (e.g., repetitive transcranial magnetic stimulation (rTMS), or both (vagus nerve stimulation)). Therefore, there remains a need to develop safe and effective treatments for the population of patients who are not adequately treated by available antidepressant medications and who suffer significant disability as a consequence.

The FDA approval of rTMS for depression a year ago was met with great enthusiasm and meta-analyses of numerous sham-controlled studies have shown rTMS to produce statistically significant antidepressant effects with few, generally mild side effects. However, these studies have also shown inconsistent and relatively modest clinical improvements in depressed patients. Therefore, there is a need to enhance the potency of rTMS for it to have a meaningful role in clinical psychiatry.

One of the most promising and innovative form of rTMS is called theta-burst stimulation (TBS). During conventional rTMS, pulses of stimulation are delivered in trains of a single arbitrary frequency (e.g., 1 Hz, 5 Hz, 10 Hz), while during TBS frequencies are coupled (usually 50 Hz coupled with 5 Hz) in ways that match endogenous neural oscillations. The theta burst pattern resembles a natural brain rhythm (such as that found in the hippocampus). This paradigm has shown to be a more potent means of enhancing cortical excitability than conventional rTMS. TBS has been used to treat some neurological disorders, such as amyotrophic lateral sclerosis, multiple sclerosis, stroke, dystonia and pain disorders, with promising results. For the treatment of psychiatric disorders, it has been used in one patient to treat negative symptoms in schizophrenia and in another to treat tinnitus associated with depression.

The current study will be a comparative trial of conventional rTMS with TBS to explore its relative efficacy to treat resistant major depression, and also to test its safety and side effects profile for this population. Finally, a noninvasive method to measure cortical excitability, called rTMS evoked potentials, will be used as a physiological marker to evaluate the effects of both treatments on the stimulated area, i.e., the dorsolateral prefrontal cortex.

Source of Funding: None.

Literature References:

Session I – 22

The Selective NK3 Antagonist AZD2624 Does Not Improve Symptoms or Cognition in Schizophrenia

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Objective: Increases in midbrain dopamine release in response to neurokinin (NK) receptor activation has led to the hypothesis that NK3 receptor antagonists have antipsychotic effects, for which there is limited clinical evidence. To test this hypothesis, we examined antipsychotic efficacy of the NK3 receptor antagonist AZD2624 in symptomatic inpatients with schizophrenia.

Methods: One hundred-six adult patients with symptomatic DSM-IV schizophrenia gave informed consent, were hospitalized in a clinical research unit, and, after up to seven days of washout from previous antipsychotic therapy, randomized to 28 days of treatment (2:2:1 ratio) with either 40 mg/D of AZD2624, placebo, or 15 mg/D of olanzapine under double-blind conditions. Afterwards, inpatients were stabilized on standard neuroleptic therapy. Endpoints were the change at 28 days in the Positive and Negative Syndrome Scale (PANSS) total score and subscales and the Clinical Global Severity (CGI-S) and Improvement (CGI-I) scales on AZD2624 versus placebo (last observation carried forward). Exploratory effects on cognition, including psychomotor ability, attention and memory, were measured using the CogState battery. Safety was assessed utilizing laboratory and electrocardiogram measures and reports of adverse events. Data was analyzed using an ANCOVA model with olanzapine used for sample validation only.

Results: There were no significant differences between AZD2624 and placebo on changes in symptom ratings (PANSS Total, LSM±SE, -3.10±3.28); Olanzapine-treated patients were significantly better than placebo (PANSS Total, LSM±SE, -13.30±3.96). Cognitive measures showed similar results.

Conclusions: Despite previous evidence, results for AZD2624 do not support the hypothesis that NK3 receptor antagonists have antipsychotic or cognitive effects in schizophrenia.

Source of Funding: AstraZeneca Pharmaceuticals, LP.

Literature References:
Validation of a Laboratory Test to Aid in the Confirmation of Schizophrenia

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Rules-Based Medicine, Inc., Austin, TX

Hypothesis: There is a set of protein biomarkers found in serum that, when measured using a panel of sensitive and precise immunoassays, produce a reproducible signature indicative of schizophrenia when compared to normal, healthy controls.

Methods: Representative serum samples were collected from patients confirmed as schizophrenia patients and matched normal controls. These samples were tested using a 189 biomarker panel from Rules Based Medicine, Inc. The data was separated using an optimal decision rule developed using blinded and unbiased process.

Results: The test detected schizophrenic samples with a sensitivity of 83% and a specificity of 83% and the signal index indicated that more than 80% of the schizophrenic patient samples were predicted to have schizophrenia with a conditional probability of over 90%.

Conclusions: A reproducible protein signature indicative of schizophrenia exists in the serum of patients with schizophrenia between first onset and five years post onset.

Source of Funding: Rules-Based Medicine, Inc., Austin, Texas.

Literature References:
Session I–25

Predictors of Response to Selective Serotonin Reuptake Inhibitors (SSRIs) in Premenstrual Dysphoria

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Background: In a prior report, we observed that women with Premenstrual Dysphoria (PMD) who failed to respond to fluoxetine (FLX) had increased free T4 plasma levels and greater sexual dysfunction at baseline compared with responders.1 We now attempt to replicate these findings in a larger sample and examine the ability of baseline clinical characteristics to predict the therapeutic response to FLX in women with PMD.

Methods: Fifty-six women prospectively diagnosed with PMD were treated with FLX (5–40 mg per day) under double-blind or open-label conditions. All women completed Visual Analog Scale (VAS) and Daily Rating Form (DRF) scales to assess the severity of PMD symptoms for at least two menstrual cycles during pretreatment baseline and after FLX. Remission was defined by the absence of clinically significant symptom cyclicity during the luteal phase after FLX. Symptom cyclicity was defined by a decrease from the mean symptomatic baseline of >30% for at least two consecutive days in any symptom (i.e., sadness, irritability or anxiety). Response was defined as a >50% improvement (relative to the symptomatic baseline) in irritability during the luteal phase after FLX. Outcome measures included the following: age, years with and age of onset of PMD, parity, self-reported premenstrual irritability and cravings, history of affective disorders (SCID), TSH/Free T4 blood levels, decreased libido (baseline and after FLX), and in a subgroup of women (n=40), estrogen receptor alpha (ESR1) genotype (previously reported to be associated with the risk of PMD).2 Differences in these measures were compared with Student’s t-test and Chi-square (for non-continuous variables) with remission or response to FLX as the between group factors.

Results: Thirty-four (60%) and 46 (82%) women with PMD met criteria for remission and response, respectively. Neither remitters nor responders were distinguished from non-remitters or non-responders by baseline characteristics, measures of decreased libido and genotype (p>0.2 for all comparisons).

Conclusions: No pre- or post-treatment clinical characteristic predicted response to FLX in women with PMD. We were unable to replicate the previously reported associations between differences in either thyroid function or sexual function and response to FLX. We recently demonstrated that a statistical descriptor of pretreatment mood rating dynamics (i.e., approximate entropy and spikiness) predicted response to GnRH agonist-induced ovarian suppression.3 In future studies, we will examine the ability of this statistical measure to predict response to FLX in PMD.

Source of Funding: National Institute of Mental Health, Intramural Research Program.

Literature References:

Session I–26

Biomarkers and Expediting Drug Development: An Interim Report on the Molecular Genetic (DRD2) Basis of Nicotine Addiction and Treatment Response


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Background: There is significant evidence suggesting that one contributor to the late-phase clinical trials challenges (and sometimes failures) is the variability between patients caused by both extrinsic and intrinsic factors, including genetics. In 2004, the Food and Drug Administration (FDA) clarified its position regarding pharmacogenomics “as a means of improving therapeutics” acknowledging the importance of “individualization factors.” The potential benefit of utilizing biomarkers to expedite and enhance the precision-of-conduct of clinical trials has not yet been fully recognized or embraced.

Methods: We enrolled 130 smokers into our IRB-approved genetic testing study pertaining to nicotine dependence, resulting from persistent cigarette smoking. Participation was voluntary, as patients were paid a total of $50.00 as reimbursement for their time and travel, in exchange for agreeing to provide one 10 ml blood sample for DNA testing. All results remained confidential; no patients were informed of their results. Additionally, none of the patients were simultaneously involved in any other clinical trial. All samples were obtained in the offices of Pharmacology Research Institute and analyzed at the University of California, Los Angeles.

Results: One hundred patients subsequently opted to enroll into one of our double-blind placebo-controlled smoking cessation drug trials, involving four different research medications. All of the patients’ samples were identified for the presence or absence of the A1 allele. In terms of smoking cessation outcomes, there was a statistically significant difference (p<0.03) in the smoking cessation success rates at the end of ten weeks of treatment, favoring active treatment over placebo in the A1-group. Furthermore, this same A1-group was also more successful at stopping smoking (p<0.05) and remaining “smoke free” at the end of ten weeks of double-blind treatment. These results were quantitatively confirmed by carbon monoxide monitoring as well.

Conclusions: These results further support the rationale for more routinely incorporating genotyping into clinical trials; they also underscore the risks of heterogeneity contributing to Type-II errors, when analyzing (Phase II or III) data. The potential clinical, regulatory and commercial benefits associated with expediting and enhancing drug development vis-à-vis the integration of biomarkers in both early- and late-stage clinical development is supported by our findings.

Source of Funding: Pharmacology Research Institute and University of California, Los Angeles.

Literature References:
Session I–27

Global Data Monitoring Program Reveals Significant Errors in the Administration and Scoring of Alzheimer’s Disease Assessment Scale-Cognitive Subscales (ADAS-cog)

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Background: The Alzheimer’s Disease Assessment Scale-cognitive subscales (ADAS-cog) is the most commonly used objective measure of cognitive change employed in dementia trials. Studies have documented variance in the administration and scoring and identified error frequency. Ongoing data quality assurance and monitoring methods minimize errors committed in clinician administered measures. Minimizing errors is paramount to reliable data. The current study investigates the number of errors identified in a data monitoring program that were not amended in the electronic data capture (EDC) during a recent clinical trial in Alzheimer’s disease.

Methods: Five hundred-ninety-seven ADAS-cog submissions were reviewed by ePharmaSolutions clinicians for administrative and scoring accuracy; 32% were determined to have at least one error in administration and/or scoring. The most significant amount of errors was found in remembering test instructions (22%), mazes (10%) and number cancellation (9%) respectively. Once an error was identified, the rater was contacted via phone or email and the scoring error was discussed and administrative and scoring conventions reviewed. When the rater agreed that a scoring error occurred, she or he was instructed to update the EDC. The clinical research associates (CRAs) received copies of all rater correspondence. Mid-study, the EDC data was reviewed against the ePS data monitoring data base for inconsistencies.

Results: Analysis of the EDC data revealed that 59% of the erroneous data had not been updated. Sites under the direction of the CRAs were instructed to update the EDC and were resent the initial correspondence describing the error. A second data base reconciliation was conducted after sites reported all updates were made and 10% of the data was found to still contain errors.

Conclusions: A reliable data monitoring program is essential for insuring ongoing data accuracy and reliability. However, data base reconciliations are necessary to ensure that identified and agreed upon errors are updated to reflect the knowledge gained by the rater through data monitoring. This knowledge must be reflected in the EDC to improve the accuracy of the data driven results.

Source of Funding: ePharmaSolutions.

Literature References:
Session I–29

The Economic Impact of Medication Access Problems

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Background: As Medicaid costs and state deficits have increased, states have continued to use prescription drug utilization management to contain costs. However, some of these approaches are associated with medication discontinuations and other access problems among psychiatric patients.

Study Aims: Assess whether Medicaid programs incur increased psychiatric emergency room (ER) and hospital costs as a result of medication access problems attributed to prescription drug coverage and management issues.

Methods: Five thousand psychiatrists in ten states were randomly selected from the AMA Masterfile. 61% responded; 34% met study eligibility criteria of treating Medicaid patients, reporting clinically detailed data on 1,625 systematically-selected Medicaid patients. Propensity score multivariate models assessed the predicted probabilities and mean number of psychiatric hospital days and ER visits, controlling for confounding clinical and sociodemographic variables including psychiatric diagnoses and symptom severity.

Results: Forty-six percent of patients had at least one medication access problem the past year, including discontinuing medications or not being able to access clinically indicated refills or new prescriptions because of drug coverage or management issues. Patients with medication access problems had a 14.4% excess predicted probability of having an ER visit (100% of p values <0.05) and an 11.9% excess predicted probability of being hospitalized (100% of p values <0.05). Across the ten states, the total expected number of ER visits was estimated to be between 44.6% and 118.5% higher among patients with medication access problems, controlling for clinical case mix. Among the majority of inpatients with 30 or fewer inpatient days, expected hospital days across the ten states ranged from 38.3% to 120.2% higher for patients with medication access problems.

Summary: Medication access problems may have significant cost-offset implications for Medicaid programs. More effective Medicaid prescription drug management and financing practices are needed to promote medication continuity and improve outcomes of treatment for psychiatric patients.

Source of Funding: American Psychiatric Foundation (APF) and the Agency for Healthcare Research and Quality (CERTS subcontract: Rutgers University). Support from APF provided through a consortium of industry supporters, including Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Forest, Janssen, Pfizer and Wyeth.

Literature References:
Soumerai SB. Benefits and risks of increasing restrictions on access to costly drugs in Medicaid. Health Affairs 2004;23:135–46.

Session I–30

The Impact of Cortisol and Brain-Derived Neurotrophic Factor on Cognitive Function in Severe Depression

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Introduction: Forty to 60% of patients meeting diagnostic criteria for major depressive disorder (MDD) have elevated serum cortisol levels and exhibit non-suppression of cortisol post-dexamethasone challenge. Elevated serum cortisol in patients with MDD has also been associated with deficits on neuropsychological testing. Recent research as shown that brain derived neurotrophic factor (BDNF) is important in promoting the development of progenitor cells in memory centers of the brain. Elevated cortisol has been shown to inhibit the synthesis of BDNF, thus, potentially interfering with neurogenesis and cognitive function (CF). Our objective was to assess the relationships of serum cortisol and BDNF on CF in severe depression.

Methods: Inpatients with MDD or bipolar disorder, depressed type (BDP) with and without psychotic features were consented to assess simultaneous measures of CF, 8 a.m. and 4 p.m., pre- and post-dexamethasone cortisol blood levels, and baseline 8 a.m. BDNF blood levels. The 17-item Hamilton Rating Scale for Depression (HAM-D-17) and the Brief Psychiatric Rating Scale (BPRS) were administered to assess severity of depression and psychosis respectively. CF was assessed using a battery of neuropsychological tests.

Results: Thirty-five subjects (40.0% female) with a mean age of 45.94±14.56 entered the study. There were seven BPD and 28 MDD; four BPD and five MDD were psychotic. Six subjects were DST nonsuppressors and 29 were suppressors. The nonsuppressors (NS) at baseline scored significantly lower on visuospatial measures than suppressors (S), mean 84.2 ± 16.81 and mean 105.23 ± 11.56 (Mann Whitney U=850, p=0.017) respectively. Baseline 8 a.m. cortisol levels were significantly higher in the NS group. 18.92±3.89 ug/dl versus 10.81±5.47 ug/dl in the S group (Mann Whitney U=16, p=0.002); there was a trend for significance at 4 p.m. These differences were independent of HAM-D-17, BPRS total, BPRS subscales. There was no difference in BDNF levels at 8 a.m. baseline between NS and S, 7.67.40±2.52 ng/ml and 6.28±2.61 ng/ml respectively. No significant relationship was found between baseline BDNF levels and CF.

Conclusions: (1) Dysregulation of cortisol was associated with lower visuospatial measures and independent of HAM-D-17, BPRS total or BPRS subscales. (2) There was no association between 8 a.m. cortisol dysregulation and 8 a.m. BDNF levels.

Source of Funding: Departmental funds, private donation.

Literature References:
Session I–31

Metabolic Effects of Olanzapine in Children with Autistic Disorder
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Background: Antipsychotics are the best-studied drugs for reducing symptoms in
tabidren with autism disorder.1 A safety concern with antipsychotics is use-
associated increases in metabolic parameters including weight, body mass index
(BMI), fasting glucose and fasting lipids (triglycerides, total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL]). These changes are associated with increased risk of cardiovascular disease and diabetes. This study examines the effect of olanzapine on metabolic parameters in a population of children with
autism who participated in a clinical trial of olanzapine.

Methods: Patients were 33 children (25 males, eight females), aged three to 11.9
years (mean, 6.58 ± 2), diagnosed with autistic disorder. The study design included a
six-week randomized, double-blind, placebo-controlled phase, followed by a six-
week open treatment phase. Responders entered a long-term open continuation
phase for an additional 20 weeks (32 weeks total study drug exposure). Safety
measures included the body mass index (BMI) and laboratory studies obtained at
baseline and Week 12. Paired t-tests were performed comparing Week 12 and
baseline values to identify any significant olanzapine associated increases in BMI z-
score, fasting glucose, and lipids. The Center for Disease Control and Prevention
BMI criteria were used to categorize children as obese (=95th percentile for BMI),
overweight (85th = x<95th percentile), healthy (5th = x<85th) and underweight
(<5th percentile).

Results: At baseline, 70.3% of children were at a healthy weight, 21.6% were
overweight, 2.7% were obese, and 5.4% were underweight. By Week 12, 42.4%
were healthy weight, 21.2% were overweight, and 36.4% were obese. Paired t-tests
comparing the BMI z-score from baseline and Week 12 showed a mean increase of
0.85 ± 0.5 which was significant (t=9.8, df=32, p=0.0000). However, there was no
clinically significant change in fasting glucose or in any of the fasting lipid
parameters. Overall, the mean increases for the lipids were: fasting triglycerides, 1.8
mg/dl; cholesterol, 3.8 mg/dl; HDL, 0.2 mg/dl; and LDL, 4.5 mg/dl.

Conclusions: The results of this study suggest olanzapine significantly increases
BMI when administered to children with autism. Other clinically significant effects
on metabolic parameters were not found in this twelve week study.

Source of Funding: Food and Drug Administration (FD-R-002190 [P.I.: Malone]),
National Institute of Mental Health (MH073524 [P.I.: Malone]). Placebo and drug
were provided by Eli Lilly.

Literature References:
1. Malone RP, et al. The role of antipsychotics in the management of beha
www.cdc.gov/growthcharts.

Session I–32

The Impact of Patients’ Expectations on Clinical Response: Re-
Analysis of Data from the Hypericum Depression
Trial Study Group
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Background: Patient belief about assigned treatment in double-blind trials may
influence outcome. We reanalyzed data from a multicenter randomized placebo-
controlled comparison trial of St. John’s wort (SJW) versus sertraline for major
depressive disorder (MDD) to determine whether patients who believed they were
receiving active therapy rather than placebo obtained greater improvement of
symptoms, independent of assigned treatment.

Methods: Three hundred-forty adults with MDD and baseline scores of 20 or
greater on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) were
randomized to either SJW 900–1500 mg/d, sertraline 50–100 mg/d, or placebo for
eight weeks. At Week 8, patients were asked to guess their assigned treatment. The
Intent-to-Treat (ITT) sample included 243 subjects with at least one post-baseline
visit for which guess data were available. Univariate factorial ANOVA was used to
determine whether there was a significant effect of treatment assignment on
clinical improvement, and whether this effect was moderated by the effect of the
patients’ guess of which medication they were taking. Chi-squared analyses
compared response (50% or greater decrease in HAMD-17) rates between the guess
groups and between the three treatment groups within each guess group.

Results: ANOVA found no significant effect of assigned treatment on clinical
improvement (p=0.65), but there was a significant effect of the patient’s guess on
clinical improvement (p<0.001). In addition, there was a significant interaction
between the two main factors (p<0.001), indicating different amounts of
improvement depending upon the particular combination of treatment received
and treatment guessed. We investigated interaction plots and tests of simple main
effects for treatment guess to better understand this interaction effect and found
that: (1) when subjects guessed they had taken placebo, clinical improvement was
uniformly small, and did not differ significantly across treatments (although
patients taking placebo showed a trend to smaller improvement); (2) when subjects
guessed they had taken SJW, treatment improvement was uniformly large, and did
not differ significantly across treatments; (3) when subjects guessed they had taken
sertraline, the response pattern was more complicated: subjects receiving placebo
and sertraline had large improvements, but subjects receiving SJW had significantly
lower clinical improvements (p=0.002). Similar findings were obtained for
treatment response rates.

Conclusions: Patient expectations regarding treatment may exert a greater
influence on clinical outcome than the actual medication received, although this
may depend upon the particular combination of treatment guessed and treatment
received. Further research into factors contributing to the observed efficacy of
antidepressants is warranted.

Source of Funding: Depression Clinical and Research Program, Massachusetts
General Hospital.

Literature References:
Hypericum Depression Trial Study Group: Effect of hypericum perforatum (St.
John’s Wort) in major depressive disorder: a randomized controlled trial. JAMA
Rutherford B, et al. Mind over medicine: the influence of expectations on
The Implications of the Cognitive Deficit Profile in Schizophrenia for Therapeutic Strategies

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Background: There is a large body of work showing a range of impairments to cognitive function in schizophrenia. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative has considered this research and proposed a number of domains of cognitive function, which are potentially treatable. For patients in on-going symptom processing, attentional vigilance to working memory, verbal/visual learning, reasoning and problem solving. However, it would be unlikely that a single therapy could treat such a diverse range of impairments; and more examination of the profiles and inter-relationships of the various cognitive deficits may facilitate the optimal targets for particular types of pharmacological therapies.

Methods: The Cognitive Drug Research Computerized Assessment System (CDR System) has been extensively used in worldwide clinical trials for over 25 years. Important features of the system are the detailed evaluation of information processing and attention, using tests of vigilance, simple and choice reaction time, as well as the precise evaluation, both in terms of accuracy and speed, of the abilities to store, retain and retrieve information from both working and episodic memory. In this paper, the profile of cognitive dysfunction in a population of patients with schizophrenia on stable medication will be closely evaluated, and will be related to the clinical severity of the condition. Further, the deficit profile of first time diagnosed previously unmedicated patients will be contrasted to that of patients on stable medication. The profile will also be compared to a range of other populations from the CDR System database.

Results: The CDR System identified a wide range of deficits in both first time diagnosed as well as patients on stable medication. The most marked deficits were to the ability to focus attention and the time taken to retrieve information held in both working and episodic memory (effect sizes >3). Deficits to focused attention, cognitive processing time and speed of retrieving information from memory are considerably greater in patients on ongoing medication, whereas the deficits to sustained attention and the time taken to retrieve information held in both working and episodic memory are unchanged. Interestingly, variability of reaction times in attention tests is less impaired in treated patients than in first time diagnosed patients. Some of these deficits are clearly related to the clinically assessed severity of the illness. The deficit profiles to attention and information processing are also compared to those seen in Dementia with Lewy bodies and Parkinson’s disease dementia, and some similarities are reported.

Discussion: This work has confirmed some previous findings with computerized tests in schizophrenia; indicating that a broader range of impairments to attention exists than is generally recognized. Further, the evidence of notably slowed retrieval of information from working and episodic memory in schizophrenia is commonly overlooked with non-automated tests. These findings may help further refine treatment strategies, particularly as similar deficits have been successfully treated in Parkinson’s and Lewy body dementia. Further, as the deficit profile differs between unmedicated and medicated patients, this may inform treatment strategies.

Conclusions: For pharmaceuticals which may not have a broad potential cognitive enhancement profile, one or more of the major deficits identified in this work could be considered as the initial therapeutic targets. However, even for those compounds, which may be expected to have broad benefits, it may be sensible to restrict the primary cognitive outcomes to one or two major domains.

Source of Funding: CRI-Worldwide.

Literature References:
Session I–35

Using Motivational Interviewing to Supplement Online Training in Exposure Therapies for Naive Clinicians

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Anxiety disorders (ADs) are the most common psychological disorder in the U.S. with approximately 28.8% of individuals being affected over a lifetime.¹ The majority of individuals with ADs do not receive even “minimally adequate” treatment.² Exposure Therapies (ETs) have considerable efficacy in the treatment of ADs. In the short term, pharmacological treatments appear to be comparably effective as ETs. However, when considering longer-term effects, ETs emerge superior having greater therapeutic gains, fewer undesirable side-effects and lower attrition rates.³

Despite the considerable evidence base for ETs, few clinicians use ETs to treat ADs. Several reasons have been proposed to explain the underutilization of ETs, including: a lack of training opportunities and the minimal impact of passive dissemination methods on changing clinician behavior. Further, even clinicians trained in ETs often do not use them to treat ADs citing concerns that ETs may be iatrogenic, not well-tolerated and overly-rigid—concerns not supported by research data.⁴

This study evaluated training methods for overcoming barriers to disseminating ETs to naive clinicians, specifically addressing the issues of negative attitudes and lack of training opportunities. We developed a media-rich, highly-interactive online training program (OLT) aimed at training clinicians in ETs and debunking myths surrounding their use. In addition, we developed a brief, supplemental Motivational Interviewing (MI) intervention focused on decreasing potential attitudinal barriers to adopting ETs (OLT+MI). We conducted a pilot randomized controlled trial (N=46) examining the efficacy of three training conditions (OLT, OLT+MI and a control OLT) in teaching naive clinicians ET. Primary outcomes included: knowledge, self-efficacy, readiness-to-adopt ET, attitudes toward ET and its perceived credibility. Participants were assessed at baseline, post-training and one-week following training.

Results indicate OLT and OLT+MI resulted in significant improvements in knowledge and self-efficacy from baseline to post-training and follow-up, whereas the control participants did not change. Both OLT and OLT+MI participants reported increased readiness-to-adopt ET, whereas controls did not. Compared to controls, OLT+MI resulted in significantly more positive attitudes toward ET and greater perceived credibility of ET at follow-up, whereas OLT alone did not. In sum, these results point to the promise of utilizing OLT as a method of training naive clinicians in ETs, especially when supplementing OLT with a brief MI intervention.

Source of Funding: National Institute of Mental Health (1R43MH082474-01A1).

Literature References:

Session I–36

Critical Time Intervention: Web-Based Dissemination of an Evidence-Based Practice

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Background: Despite a growing body of evidence about best practices for vulnerable populations, a research-practice gap persists in many social service settings. Specifically, direct service providers who work with individuals experiencing homelessness do not always have access to the best evidence on what is effective for helping individuals with serious mental illness to exit homelessness permanently. Critical Time Intervention (CTI) is an evidence-based practice proven to reduce recurrent homelessness amongst mentally ill individuals who have a history of homelessness.⁵ The authors of this study developed and tested an eight-week, multi-media web-based training strategy that relied on a peer-based learning model, the Community of Practice, to teach Critical Time Intervention to help these providers bridge the gap between research and practice.

Methods: A diverse group of 27 social service practitioners who serve homeless clients were recruited from agencies across the U.S. to complete this online training. An exploratory study incorporated both quantitative and qualitative measures in open-ended interviews with these participants to: (1) assess the impact of the CTI curriculum and web-based, interactive learning technology model of training with three groups of practitioners—social workers, clinical social work supervisors and other social service staff; and (2) describe factors which influence practitioners’ interest in and ability to incorporate evidence-based practices and CTI in their work with clients who are homeless and/or at risk of homelessness.

Results: Combining internet-based interaction with a community of practice allowed participants to learn within the context of their jobs and fostered learning relationships amongst participants and trainers. Our pre-post study revealed very high percentages of this diverse group of providers attained and retained knowledge of various aspects of the CTI model. Additionally, a large majority reported that they shared what they learned with colleagues (96%), affirmed or increased their interest in learning evidence-based practices (72%), changed the way they work with homeless clients (80%), and began to actively work to implement CTI in their agency (80%) as a result of this training experience. Those factors most apt to contribute to successful outcomes included the peer interaction provided by the Community of Practice model and the multiple approaches provided to help participants apply their knowledge of the CTI model to their own work and the populations they serve.

Conclusions: Findings from this pilot study suggest web-based training may be an effective way to equip homeless service providers to implement evidence-based practices.

Source of Funding: National Institute of Mental Health (R01MH59716 and HHSN271200800027C). Additional support provided by the New York State Office of Mental Health.

Literature References:
**Session I–37**

**NeuroVisions: Teaching Neuroscience with Neuroimaging Data**

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**Introduction:** This poster presentation describes development and testing of an e-Learning module for advanced undergraduate instruction: Seeing GABAA Receptors at Work—Quantifying Radioligand Binding and Its Modulation by Endogenous Signaling Molecules. In the module, students investigate allosteric regulation of GABAA receptors through image analysis of in vitro receptor autoradiography. A video review of the module is available on YouTube.com at http://www.youtube.com/watch?v=dKoCgy_z0Yc. Developed by Science Approach, this Moodle-based course is the prototype for a series of six e-Learning modules.

**Background and Significance:** The scientific merit and significance of this presentation derive from the process and theory utilized to create the prototype: the scaffolded pedagogical structure that guides undergraduate students through understanding and replicating neuroscience research conducted by Miles Orchinik, Ph.D.; online implementation of a sophisticated Java-based image analysis tool (ImageJ-A) used by students to gather data from research images; online implementation of “RI,” the statistical package used by students to analyze the imaging data; and research methods employed to pilot test the prototype with faculty, scientists and undergraduate students at professional meetings.

**Methods:** For the research summarized in this presentation, approximately 200 neuroscience faculty, graduate students, and research scientists were surveyed from a commercial exhibit hosted at two Society for Neuroscience (SFN) meetings. At the 2008 meeting, respondents completed a computer-based survey that included samples of the prototype being developed by the project. At the 2009 meeting, respondents viewed a movie presentation of the prototype and were recruited to complete an online survey at another time. A reasonably representative sample of SFN participants was developed in this manner.

**Results and Conclusions:** Pilot testing of the prototype module at the SFN meetings indicated that the pedagogical approach, image and statistical analysis technology, visual nature of the module, immersion in real research and subscription-based system for delivering the e-Learning content were well-received by the respondents. The pilot research revealed that faculty from small undergraduate institutions particularly valued access to imaging technology not available on their campuses. Pilot-test results affirmed the general structure and purpose of the NeuroVisions modules and the findings were used to inform development and classroom-testing of all the prototype module.

**Source of Funding:** National Institute of Mental Health (2R44MH070250-02).

**Literature References:**

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**Session I–38**

**Brief Depression Screener Developed Using Item Response Theory (IRT) for Antenatal and Postpartum Women**

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**Background:** Approximately 320,000 to over one million women in the U.S. experience symptoms of perinatal depression each year.1,2 Estimates of antenatal depression are harder to obtain due to the lack of appropriate diagnostic criteria. Despite this, no screening tool exists that was developed and tested with both antenatal and postpartum women, analyzed using Item Response Theory (IRT), and that contains concise, simple language and a consistent response option set.

**Methods:** A careful review of current gold-standard measures of depression, both general and perinatal, was undertaken (e.g., the Beck Depression Inventory-II [BDI-II], the nine-item Patient Health Questionnaire [PHQ-9] and the Edinburgh Postnatal Depression Scale [EPDS]). Items were grouped by core concept and rewritten to omit lead phrases, contingencies, multiple concepts and idiomatic language as well as conform to a “past seven days” timeframe and a consistent five-point Likert response scale. The refined item pool contained 159 general depression items, as well as 73 items relevant to perinatal issues surrounding depression (e.g., social support, relationship with baby). Items were reviewed by a panel of depression and obstetric care experts, rated on a three-point Likert scale for clarity and centrality, and subsequently administered using cognitive interviewing techniques to 20 antenatal and ten postpartum women exhibiting a range of scores on the EPDS.

**Results:** Items rated higher than 2.5 on average were retained. Qualitative analysis of cognitive interviewing results indicated that sleep, appetite, and energy symptoms do not characterize perinatal depression. Overall, approximately 22% of general depression items and 25% of antenatal and postpartum questions were omitted. A final pool of 67 general depression items and 44 perinatal items (12 antenatal and 32 postpartum) were retained for quantitative validation.

**Conclusions:** Items retained are currently being validated against the BDI-II, PHQ-9, EPDS, Patient-Reported Outcomes Measurement Information System (PROMIS) depression items, and an abbreviated form of Module A (Mood Episodes) of the Structured Clinical Interview for DSM-IV-TR Axis I Diagnoses (SCID) in a sample of 500 antenatal and 500 postpartum women from both private and public sector sites. IRT analyses will be conducted on the newly developed and validated depression items. Given that results from cognitive interviewing illustrate that a subset of general depression symptoms included in current postpartum depression measures are not closely related to perinatal depression, we believe that the ten-item screener and a 20-item questionnaire being developed, and available free-of-charge, will be more precise than existing perinatal depression measures.

**Source of Funding:** In part by the National Institutes of Health (MH082485: TeleSage, Inc).

**Literature References:**
A Flexible, Web-Based System for the Administration of Computer Adaptive Tests

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Introduce: Computerized adaptive testing (CAT) within an item response theory (IRT) framework is a powerful methodology for behavioral measurement. CAT can substantially reduce respondent burden without compromising reliability. CAT is a tailored assessment approach that uses information from each item response to select an optimal item to administer next. The adaptive approach can yield reliable estimates with significantly fewer items than are included on a fixed-length questionnaire.

A CAT must have access to a bank of items with known properties. Item properties, defined by item parameters in the IRT framework, contain information about item reliability and severity. Once item parameters have been obtained, IRT-based scores produced from any subset of those items are immediately comparable. In an adaptive setting, with a large enough item bank, two individuals will have few, if any, items in common. By using IRT-based parameter estimates, adaptive tests are able to obtain scores which are comparable even while using different items. By using these item parameters and adjusting the test based on the respondents’ behavior, it is possible to achieve comparable reliability to static forms with 1/3 to 2/3 fewer items. This can greatly reduce respondent burden or allow of the collection of more information in a fixed time window.

Despite the measurement advantages and the increased interest in IRT CAT, there have been few implementations of CAT methodology for assessment of non-educational constructs; the technical rigor required for CAT creation and implementation has limited its uptake in the broader research community. The system being debuted here was designed to overcome this difficulty by providing a user-friendly, flexible web-based CAT platform.

Current System: A prototype web-based CAT platform that can be customized to a client’s specifications has been completed. The system can administer multiple client-specific adaptive tests via the internet. The system currently supports unidimensional and bi-factor IRT models with polytomous item responses. IRT-based scores can be supplied to the client via a data file (including raw item-level data) or via the computer screen at the completion of a given CAT.

Future Directions: Ongoing developments are underway to significantly expand the flexibility of the system. Some of these developments include: expanded administrator interface and controls, expanded IRT models including full multidimensional IRT models, a test assembly center with simulator and the incorporation of differential item functioning.

Source of Funding: National Institute of Mental Health (1R43MH085400-01A1). Literature References:


Session I–40

Utilizing Web-Based Education and Networking Tools to Enhance Geriatric Mental Health Research Mentoring and Career Management

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Background: By 2030, approximately 20% of the population will be over age 65, and it is predicted that one-fifth of the older population will have a mood, anxiety or psychotic disorder. Mental disorders threaten functional independence and quality of life, and are associated with increased use and costs of acute and long-term care. In 2008, the Institute of Medicine released a report recommending increased support for research into new models of care for older adults as well as increased recruitment and retention of junior faculty who will research and implement evidence-based practices in geriatric mental health.

Methods: A trio of web sites targeting new investigators was created to address this need. MedEdMentoring.org is a mentoring and career development initiative providing tools and resources for junior investigators building careers in geriatric mental health research and senior investigators who mentor them. CommunityGHMResearch.org presents translational research—via educational modules and interactive presentations presented by leaders in the field—that focuses on building and implementing mental health interventions for older adults in community settings. The MedEd Seminar Web site provides a customizable and dynamic Web-based platform where these researchers can share and store information and resources, conduct live seminars, and collaborate on research projects and grant proposals with the goal of obtaining independent research funding.

Results: From November 2005 to December 2009, MedEd Mentoring received 20,308 unique visitors. To date, MedEd Seminar has hosted over 50 live seminars for workgroup members, and 47 investigators have participated in CommunityGHMResearch.org’s monthly online seminars. Although created in succession and independent of each other, the Web sites are cross linked and a core group of users have utilized all three sites.

Conclusions: This network of web sites provides junior- to senior-level investigators with peer-reviewed resources, networking software, and information and mentorship from academic leaders at the front line of mental health services research. The collective community of users benefit from learning about and sharing current information about research and interventions in the field and as well as gaining feedback from mentors about proposed research projects in order to better their chances of obtaining independent research funding and feed the geriatric mental health research pipeline.

Source of Funding: National Institutes of Health (HHSN271200664098C, HHSN271200774105C, and HHSN278200444084C). Literature References:

Session I–41

Novel Vasopressin 1a Antagonists as Potential Drugs for Depression

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Background: Existing drugs for depression are not uniformly effective, frequently have undesirable side effects and, according to recent estimates, do not help 50% of depressed individuals. Antidepressants with novel mechanisms of action could improve treatment outcomes. Vasopressin (AVP) antagonists that selectively bind to the central nervous system (CNS) V1a or V1b receptor subtypes appear to be strong candidates for such a role. Azevan has developed novel AVP 1a (V1a) antagonists that are orally available and efficacious in preclinical models of depression. Two compounds are in the clinic: SRX251-HCl, which completed Phase I single ascending dose and five-day repeat multiple ascending dose clinical trials, and SRX246-HCl, where FIH trials are in progress. Phase I clinical trial results are presented.

Methods: Institutional Review Board approval was obtained for all studies. SRX251 was tested for safety, tolerability and pharmacokinetic profiles of single (20–240 mg) and multiple (120 mg b.i.d) compared to placebo when given to healthy volunteers using double-blind, placebo-controlled, single-center, randomized, ascending dose studies. SRX246 also was tested for safety, tolerability and pharmacokinetics. In the single ascending dose (SAD) arm, subjects received oral placebo or SRX246 (40–520 mg). Preliminary safety results are available and a multiple ascending dose (MAD) study is planned.

Results: For SRX251, PK results showed dose-related increases in Cmax and AUC in the SAD and MAD studies. With BID repeat dosing, a 1.7-fold accumulation was observed on Day 5 with an increase in 1/2 to 16 hours versus nine hours at the maximum tolerated dose (MTD) 180 mg) in the SAD segment. SRX251-HCl was safe and well-tolerated. No clinically significant changes in vital signs, physical exams, laboratory tests or electrocardiograms were observed. All adverse events (AEs) were either mild or moderate. No serious AEs were reported. Mild/moderate gastrointestinal (GI) disturbance was the dose-limiting toxicity at 240 mg in the SAD study and was reduced in frequency and mild when SRX251-HCl was given in divided doses (120 mg b.i.d). For SRX246, the compound was safe and well-tolerated at single doses up to 240 mg. At 320 mg, mild/moderate GI disturbance was observed and was considered dose-limiting.

Discussion: The results for SRX251-HCl demonstrate an excellent safety profile with very good tolerability, plasma levels and PK. The SAD safety results for SRX246 to date follow a comparable pattern. These novel V1a antagonists potentially represent a new pharmacotherapy for depression and other stress-related affective disorders. Phase II proof-of-concept clinical trials are anticipated in late 2010/early 2011.

Source of Funding: National Institute of Mental Health and National Institute of Child Health and Human Development (SBR Phase I, Phase II, and Phase II Competing Continuation grants [HD37239, MH063663]), Ascent Biomedical Ventures, LP, Azevan Pharmaceuticals, Inc.

Literature References:

Session I–42

Comparing Mixed-Effect Model Repeated Measures (MMRM) versus Last Observation Carried Forward (LOCF) Statistical Methods in a Six-Week Placebo- and Active-Controlled Trial of Iloperidone for the Treatment of Schizophrenia

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Background: Pivotal trials are designed primarily for regulatory purposes; the FDA has historically used last observation carried forward (LOCF) statistical methodology. Recently, mixed-effect model repeated measures (MMRM) analysis has been accepted as an analytic choice. MMRM addresses the entire intent-to-treat (ITT) study population. Unlike LOCF, it considers the time of dropout and estimates the course of symptoms after dropout instead of carrying the last assessment forward. We compared these two analyses in a phase III pivotal trial (Study ILOS22 3005) that was part of the Food and Drug Administration (FDA)’s review of the recently approved atypical antipsychotic iloperidone.

Methods: Patients aged 18–65 years with a DSM-IV diagnosis of schizophrenia with acute/subacute exacerbations and a Positive and Negative Syndrome Scale Total (PANSS-T) =60 were randomized to double-blind iloperidone (12–16 mg/d or 20–24 mg/d), risperidone 6–8 mg/d, or placebo for six weeks. Outcomes included Brief Psychiatric Rating Scale (BPRS), PANSS-T, and PANSS positive and negative subscale scores. Like the FDA review, this analysis is confined to schizophrenia patients (n=521). A repeated measures analysis of covariance (MMRM) with treatment, week and treatment-by-week as factors and baseline as a covariate on the ITT population using the observed-case approach was compared to LOCF.

Results: BPRS least squares mean changes (with standard error) after 6 weeks of treatment, using LOCF and MMRM were: 7.4(1.00) and 9.9(1.06) for iloperidone 12–16 mg/d, 8.8(1.21) and 10.3(1.27) for iloperidone 20–24 mg/d, risperidone 6–8 mg/d, or placebo for six weeks. Outcomes included Brief Psychiatric Rating Scale (BPRS), PANSS-T, and PANSS positive and negative subscale scores. Like the FDA review, this analysis is confined to schizophrenia patients (n=521). A repeated measures analysis of covariance (MMRM) with treatment, week and treatment-by-week as factors and baseline as a covariate on the ITT population using the observed-case approach was compared to LOCF.

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Conclusions: LOCF and MMRM yielded similar statistical results in iloperidone efficacy versus placebo, but the magnitude of the effect was larger with MMRM. MMRM may be a more clinically relevant method for evaluating efficacy. These findings are consistent with those from other iloperidone trials.

Source of Funding: Novartis Pharmaceuticals Corporation.

Literature References:

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Session I–43

The Effects of Olanzapine on QTc in Children with Autistic Disorder

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Background: Antipsychotics are the best-studied drugs for reducing disruptive symptoms such as irritability, hyperactivity and mood lability in children with autistic disorder. A safety concern with antipsychotics is that administration can be associated with prolongation of the QTc, an electrocardiographic measure of ventricular depolarization and re-polarization. QTc prolongation greater than 60 msec from baseline or an absolute QTc of greater than 500 msec have been associated with ventricular arrhythmias and sudden death. Olanzapine has not been shown to prolong QTc in adults. However, the effect of olanzapine on this important index is not well studied in children. To examine the effect of olanzapine on QTc in a population of children with autism who participated in a clinical trial of olanzapine monotherapy.

Methods: Patients were 35 children (26 males), aged three to 11.9 years (mean, 6.3 ± 2), diagnosed with autistic disorder. The study included a six-week randomized, double-blind, placebo-controlled phase, followed by a six-week open treatment phase. Responders at the end of the open treatment phase continued to receive open olanzapine for an additional 20 weeks. Electrocardiograms (ECG) were obtained at baseline, Week 12, and Week 32. They were obtained in a fasting state between 9 and 10 a.m., when drug was at its trough level. To investigate whether there were olanzapine-associated QTc increases, paired t-tests were performed.

Results: The mean QTc at baseline was 409.3 ± 19.1 msec, at Week 12 was 407.3 ± 25.2 msec, and at Week 32 was 411.3 ± 40.1 msec. The change in QTc from baseline to Week 12 was -2.1 ± 29 msec (t=0.02, df=34, p=0.68), and from baseline to Week 32 was 2.28 ± 42.7 msec (t=0.226, df=17, p=0.824). No child had a QTc greater than 500 msec during this study. One child with a baseline QTc of 388 msec had an increase of 260 msec at Weeks 12 and 32.

Conclusions: These results suggest that olanzapine monotherapy does not significantly affect QTc when administered to children with autism.

Source of Funding: Food and Drug Administration (FD-R-002190M P.J.: Malone) and National Institute of Mental Health (MH073524, P.J.: Malone); placebo and drug were provided by Eli Lilly.

Literature References:

Session I–44

A Pilot Study of Lamotrigine Adjunctive Therapy to Lithium and Divalproex in Depressed Patients with Rapid Cycling Bipolar Disorder and a Recent Substance Use Disorder: A 12-Week, Double-Blind Placebo-Controlled Trial

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Background: In the National Comorbidity Survey Replication, 60% of patients with bipolar I disorder and 40% with bipolar II disorder had a lifetime history of substance use disorder(s) (SUDs). In our previous studies, a third of patients with rapid cycling bipolar disorder (RCBD) had a recent history of SUDs and about 21% of them responded to the combination of lithium and divalproex. This study was under-taken to investigate the efficacy and safety of adjunctive lamotrigine in RCBD and a recent SUD(s) who were non-responsive to the combination of lithium and divalproex.

Methods: Extensive Clinical Interview, the Mini International Neuropsychiatric Interview (MINI), and the Structured Clinical Interview for DSM-IV Axis I Disorders—substance use disorder module were used to ascertain DSM-IV diagnosis of RCBD, SUDs, and other Axis I disorders. Following up to 16-weeks of open-label treatment with lithium plus divalproex, patients who did not meet criteria for bimodal response as measured by Montgomery-Asberg Depression Rating Scale (MADRS) less than 19, Young Mania Rating Scale (YMRS) less than 12 and Global Assessment of Functioning (GAF) greater than 51 for four weeks were randomized to a 12-week, double-blind addition of lamotrigine or placebo to lithium and divalproex. The primary outcome was the change in MADRS total score from baseline to endpoint. The analysis was based on the intent to treat sample. Chi-square or t-test was applied where appropriate.

Results: Of 98 patients enrolled into the study, 36 were randomized to receive lamotrigine (n=18) or placebo (n=18) and eight patients per arm completed the study. Eight of ten patients in each arm discontinued the study due to lack of efficacy. No patient in either arm discontinued due to adverse events. The change in MADRS from baseline to the end of study was -9.1 plus or minus 11.2 among lamotrigine-treated patients versus -4.5 plus or minus 13.1 among placebo-treated patients (p=0.27). There were no significant differences in changes in YMRS and Clinical Global Impressions Scale scores. Rates of response (38.9% versus 33.3%) and remission (27.8% versus 27.8%) were similar for lamotrigine- and placebo-treated patients, respectively. There were no significant differences in common adverse events including tremors, diarrhea, nausea, headache and dry mouth.

Conclusions: Lamotrigine adjunctive therapy was well tolerated in patients previously non-responsive to initial treatment with the combination of lithium plus divalproex. Although a clinically meaningful difference in MADRS score reduction was observed in lamotrigine-treated patients over those receiving placebo, the study was underpowered to detect statistical significance. A larger study appears warranted to determine if adjunctive lamotrigine is superior to placebo for reducing depression severity in RCBD accompanied by a co-occurring SUD.

Source of Funding: Stanley Medical Research Institute.

Literature References:
Session I–45

Neurobehavioral Effects of Interferon-Alpha in Patients with Hepatitis C: Phenomenology and Paroxetine Responsiveness of Symptom Dimensions

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Background: The cytokine interferon-alpha (IFN), a stimulator of innate immunity, is used to treat patients with cancer and causes profound behavioral alterations. Using dimensional analyses, we have previously shown the expression and treatment responsiveness of two neuropsychiatric symptom clusters in patients with malignant melanoma during their first three months of high-dose IFN therapy: a neurovegetative syndrome and a mood and anxiety syndrome. We sought to determine whether similar symptom complexes would arise in patients with hepatitis C administered lower doses of pegylated or non-pegylated IFN/ribavirin during six months of time.

Methods: As previously published, study participants with hepatitis C were randomly assigned to receive either paroxetine (10 mg per day) (n = 28) or placebo (n = 33) in a double-blind design. Patients remained on study medication for 26 weeks unless they dropped out or were terminated from the study. Patients were evaluated at baseline and every four weeks of IFN/ribavirin treatment thereafter. Neuropsychiatric assessments included the 10-item Montgomery Åsberg Depression Rating Scale (MADRS). To perform the dimensional analyses, neuropsychiatric and neurovegetative symptoms of the MADRS were grouped into four symptom complexes corresponding to depression, anxiety, cognitive dysfunction, and neurovegetative symptoms (such as fatigue, insomnia, and anorexia). For each patient, the mean score of each dimension was calculated using the average of the sum of relevant items from the MADRS scale. Analysis of variance with treatment (placebo versus paroxetine) as the independent factor and time as the repeated measure factor were performed for mean comparisons.

Results: As IFN/ribavirin treatment proceeded, depression, anxiety, cognitive dysfunction, and neurovegetative symptoms increased, with the placebo-treated group demonstrating a higher mean score for depression and anxiety symptom complexes. Depressive symptom scores were significantly lower in the paroxetine treatment group over time (p = 0.04).

Conclusions: Symptoms of depression were more responsive, whereas anxiety, cognitive dysfunction, and neurovegetative symptoms were less responsive, to paroxetine treatment. This study replicates our previous findings in patients with malignant melanoma receiving IFN, i.e., that there is a distinct phenomenology and treatment responsiveness of symptom dimensions induced by IFN, and suggests that different mechanisms mediate the various behavioral manifestations of cytokine-induced “sickness behavior.”

Source of Funding: Schering-Plough and GlaxoSmithKline; National Institute of Mental Health (MH60723, MH64619, MH00680, MH71580); National Institutes of Health/ National Center for Research Resources General Clinical Research Center (M01 RR00039).

Literature References:

Session I–46

Performance in Practice Clinical Tools for Post Traumatic Stress Disorder

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Introduction: In current practice, clinicians are expected to maintain expertise in the face of an ever-expanding evidence base. However, traditional didactic approaches to continuing education have shown limited success in changing practice; a number of studies have demonstrated that a substantial gap still remains between recommended evidence-based best practices and actual clinical practice. Clinical practice guidelines provide clinicians with a valuable resource by compiling and synthesizing the most recent scientific knowledge and expert consensus, and are a rich fund of state-of-the-art information. However, they are difficult to translate and apply at the concrete patient or organizational level because their traditional narrative format does not provide clinicians with immediate opportunities to appraise and assimilate scientific evidence. Hence, new methods are needed.

Methods: To speed the adoption of evidence-based care into clinical practice and in response to the American Board of Medical Specialties and the American Board of Psychiatry and Neurology Maintenance of Certification (MOC) clinician self-assessments requirements, the American Psychiatric Association clinical and research teams collaborated to develop two prototype sets of Performance in Practice (PiP) clinical self-assessment tools, guided by evidence-based recommendations from the latest practice guidelines. The first set of tools was aimed at the management of depression; the second set focused on the management of post traumatic stress disorder (PTSD) and is the focus of this poster. The PiP tools have multiple applications. In addition to helping clinicians prepare for MOC self-assessment requirements through chart reviews and real-time evaluation of new or existing patients, the tools can be used to inform improvement efforts at the clinician, practice- or systems-level and facilitate detection of potential gaps in evidence-based care. The PiP tools provide clinicians with active learning experiences by translating conceptual information from practice guidelines into practical steps, thus supporting integration of evidence-based best practices into clinical care. These tools are applicable beyond psychiatry, as they can be used for self-assessment by other provider groups to support improvement activities for PTSD care.

Conclusions: The PiP tools have the potential to change the way new scientific information is disseminated and adopted in routine practice, and to improve rehabilitative approaches for individuals suffering from PTSD. Successful implementation of the PiP approach in clinical practice could have substantial impact on facilitating quality improvement efforts, thus lessening the current gap between evidence-based practice recommendations and actual care.

Source of Funding: In part by the Department of Defense (W81XWH-08-1-0399); and the American Psychiatric Foundation.

Literature References:
The Stanley Neuropathology Consortium Integrative Database: A Novel, Web-Based Tool for Exploring Molecular Targets for Therapeutic Drugs for Psychiatric Disorders and Pathways Associated with Those Targets

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Currently approved antipsychotic drugs produce varying degrees of symptom amelioration in most patients but often cause unwanted side effects. All of the atypical antipsychotics bind multiple targets such as dopamine D2 receptor, 5-HT2 receptors, α2-adrenergic receptor and muscarinic receptors. Identifying deficits in the target receptors and their associated pathways in the brain tissues of psychiatric patients may lead to the development of drugs with increased efficacy and fewer side effects.

We explored the targets of the current atypical antipsychotics and associated pathways using the Stanley Neuropathology Consortium Integrative Database (SNCID). The first module of the SNCID which includes 1749 neuropathological markers measured in 12 different brain regions in 60 human subjects (15 each schizophrenia, bipolar disorder, depression and unaffected controls) and genome-wide expression microarray datasets enable users to explore abnormal neuropathology markers and pathways associated with these markers in various brain regions.

Total dopamine levels were significantly increased in the prefrontal and cingulated cortices of schizophrenia patients, while D2 receptor mRNA levels were significantly reduced in the prefrontal cortex of subjects with schizophrenia and depression. There was no significant change in 5-HT2 receptor mRNA levels in the prefrontal cortex of subjects with major psychiatric disorders. However there was a significant decrease of the receptor in the hippocampus of subjects with schizophrenia and bipolar disorder. Moreover, 5-HT2A receptor mRNA levels were negatively correlated with antipsychotic treatment. While α2-adrenergic receptor activity was significantly reduced in the prefrontal cortex of subject with schizophrenia, depression and bipolar disorder, there was no significant change in mRNA levels of the receptor. Muscarinic, M1/M4, receptors were significantly reduced in the cingulate cortex of schizophrenia patients. Genes belonging to several biological processes including oligoden-drocytes, sensory perception and nervous system development were commonly associated with D2 receptor and α2-adrenergic receptors in the prefrontal cortex. In addition, genes belonging to DNA and RNA metabolic processes were specifically correlated with D2 receptor expression.

Our analysis indicates that there are brain region specific deficits in the target receptors of the current atypical antipsychotic drugs in subjects with major psychiatric disorders. Moreover, biological pathways commonly or specifically associated with these target receptors are identified. With the addition of the new module for the Stanley Neuropathology Consortium (SNP) association analysis, which is currently under development, the SNCID will be a useful tool for the validation of existing targets and the identification of better novel targets for the treatment of major psychiatric disorders.

Source of Funding: Stanley Medical Research Institute

Literature References:
Noninvasive Neuromodulation with Trigeminal Nerve Stimulation: A Novel Treatment for Major Depressive Disorder

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Background: Modulation of brain activity via stimulation of the Trigeminal Nerve (TNS) is an emerging therapy for epilepsy, with excellent safety profile and significant reductions in seizures in pilot studies in subjects with medically refractory epilepsy.¹² 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. In this proof-of-concept project, the effects of TNS on depressive symptoms were examined in major depressive disorder (MDD) as an adjunct to pharmacotherapy.

Methods: Five adults (age 31–59, mean 49.6 (10.9 s.d.), 3F:2M) with non-psychotic unipolar MDD were studied to date in an eight-week open label outpatient trial at an academic medical center. Current episodes were of >4 months duration, with nonresponse to at least one antidepressant over at least six weeks during the current episode, and concomitant use of at least one antidepressant. All had prominent residual symptoms, with mean Hamilton Rating Scale for Depression (HAM-D-28) scores at study entry of 22.4 (3.9 s.d.), range 19 to 29. Subjects placed stimulating electrodes over the supraorbital branches of the trigeminal nerve for at least eight hours per day (primarily while asleep), with current adjusted to maximal comfortable levels. All five completed the trial. Primary outcome was change in HAMD at eight weeks.

Results: TNS was well tolerated, no serious adverse events occurred during the eight-week treatment period. Decreases in HAMD-28 scores were significant, from 25.4 (3.9) at entry to 13.6 (6.3) at Week 8 (2-tail t-test p=0.01, Cohen’s d 2.4). Responses on the Beck Depression Inventory similarly declined, from 26.8 (8.1) to 10.6 (4.9) (p<0.01, d 2.3). Increases on the 16-item clinician-rated Quick Inventory of Depressive Symptomatology were also significant, decreasing from 10.8 (3.4) to 5.5 (4.4) (p<0.05, d 1.3).

Conclusions: Significant decreases in depression severity were achieved in the eight weeks of acute TNS treatment. This novel approach to brain stimulation may have use as an adjunct to pharmacotherapy in depression. Additional examination in a larger sample will be needed to delineate efficacy and tolerability with greater reliability.

Source of Funding: University of California, Los Angeles.

Literature References:

Association between Anxiety and Bipolar I Disorder in Randomized, Placebo-Controlled, Maintenance Study of Ziprasidone Combined with Mood Stabilizer

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Background: Anxiety is common in bipolar disorder and can influence illness course. We conducted a post-hoc investigation of relationships between comorbid anxiety and response to ziprasidone (80–160 mg/d) combined with a mood stabilizer (lithium or valproic acid) (ZIP+MS) in bipolar 1 disorder (BPI).

Methods: During open-label stabilization, 584 DSM-IV BPI patients received up to four months of ZIP+MS. Patients achieving >8 weeks clinical stability were randomized to up to six months of double-blind treatment ZIP+MS (57 ZIP+Li; 70 ZIP+VPA) versus placebo+MS (49 PBO+Li; 63 PBO+VPA). We explored relationships between anxiety symptoms, using five anxiety items (worry, somatic anxiety, psychotic anxiety, phobia, obsessions/compulsions) on the Schedule for Affective Disorders and Schizophrenia-Bipolar (SADS-B) and mood responses.

Results: During open-label stabilization, SADS-B Mania Rating Scale (MRS) improvement (mean -13.5, SD 9.6) was inversely associated with severity of pre-existing anxiety (p<0.01). Among 330 patients with lower pre-treatment anxiety (score <2 on all five SADS-B anxiety items), 262 remitted (79%) by Week 16, compared to 155 of 220 (70%) with higher pre-treatment anxiety level (score ≥2 on at least one SADS-B anxiety item) (p<0.05). Among subjects with higher pre-treatment anxiety, 77% (93/121) remitted in the ZIP+VPA group compared to 62% (57/92) in the ZIP+Li group (p=0.03). Remission rate was similar for ZIP+VPA (77%) and ZIP+Li (82%) in subjects with lower pre-treatment anxiety (p=0.30). Thus, among patients receiving ZIP+Li (but not ZIP+VPA) those with higher compared to lower pre-treatment anxiety had a significantly lower remission rate (p<0.05). During double-blind treatment, ZIP+Li/VPA versus PBO+Li/VPA effects differed between lower versus higher baseline (pre-randomization Week 16) anxiety groups, and the adjunctive mood stabilizer used (Li N=106 versus VPA N=133) (p=0.05). Among subjects with lower baseline anxiety, those receiving PBO+Li/VPA had a higher rate of intervention for mood episode (32%, 33/103) compared to those receiving ZIP+Li/VPA (19%, 21/111) (p=0.05), with those receiving PBO+Li having a higher rate of intervention for mood episode (45%, 20/44) compared to those receiving ZIP+Li (18%, 9/49), ZIP+VPA (19%, 12/62) and PBO+VPA (22%, 13/59) (p<0.001). Among subjects with higher baseline anxiety, those receiving PBO+Li/VPA had a higher rate of intervention for mood episode (44%, 4/9) compared to those receiving ZIP+Li/VPA (25%, 4/16) (p<0.01), with a significant Li versus VPA differences.

Conclusions: ZIP+MS compared to PBO+MS maintenance was more effective, in both high and low pre-treatment anxiety groups. Lower pre-treatment anxiety may indicate particular preventive benefit with ZIP+Li compared to PBO+Li.

Source of Funding: Pfizer, Inc.

Literature References:
Validation of an Electronic Columbia-Suicide Severity Rating Scale Using Interactive Voice Response Technology

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A computer-automated version of the Columbia–Suicide Severity Rating Scale (eC-SSRS) using interactive voice response technology was evaluated. The eC-SSRS assesses lifetime suicidal ideations and behaviors at baseline and prospectively monitors such ideations and behaviors thereafter. Ten control volunteers and ten psychiatric inpatients were administered the C-SSRS at baseline and four to eight days later by two experienced clinical trial raters. Subjects also used touch-tone telephones to complete the eC-SSRS. Paper forms of the Beck Scale for Suicide Ideation (BSS) and study feedback documents were also completed. Kappa measures of agreement compared inter-rater reliability between the human C-SSRS administrations and compared the C-SSRS results with the obtained eC-SSRS data. Convergent validity with the BSS was also evaluated. Twenty baseline and nineteen follow-up assessments were completed. No suicidal ideation was identified by either the C-SSRS or eC-SSRS in 28 of 39 assessments. Agreement between the eC-SSRS and either C-SSRS rater was comparable or superior to the agreement between the two C-SSRS raters. Nonparametric concordance (Kendall’s tau) with BSS scores supported convergent construct validity of the C-SSRS and eC-SSRS; patient feedback and expressed personal preferences supported the feasibility and validity of the eC-SSRS for assessing suicidality. The reliability and validity of the C-SSRS and eC-SSRS for assessing suicidal ideation and behaviors were comparable in this study, supporting the feasibility and validity of the eC-SSRS for prospectively monitoring suicidality in clinical trials or clinical care.

Source of Funding: GlaxoSmithKline, eResearchTechnologies.

Literature References:

Effect of Aripiprazole Adjunctive to Antidepressants on Sexual Functioning: A Subgroup Analysis of a 52-Week Open-Label Safety Study (CN138-164)

Anita H. Clayton, M.D.1; Ross A. Baker, Ph.D. M.B.A.2; Carlos Rojas-Fernandez, Ph.D., Robert A. Forbes M.D.1; James Eudicone, M.S., M.B.A.2; Robert M. Berman, M.D.3


Background: Sexual dysfunction is frequently associated with major depressive disorder (MDD) and is possibly related to psychiatric or medical conditions, substances, psychosocial changes and antidepressant therapy (ADT) itself. This analysis evaluated the impact of long-term (up to 52 weeks) open-label treatment with aripiprazole adjunctive to ADT on safety, tolerability and sexual function and efficacy measures in patients with MDD.

Methods: Data were analyzed post hoc from de novo patients enrolled in an open-label safety study of adjunctive aripiprazole after documented inadequate response to one or more ADT. Three classes of ADT were included: selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), which potentially inhibit sexual function; and a norepinephrine dopamine reuptake inhibitor (NDRIs), bupropion which potentially improves sexual function.

Global well-being after adjunctive aripiprazole treatment was assessed using the mean change in the Clinical Global Impressions Scale-Severity rating (CGI-S) score from baseline to Week 52 [last observation carried forward (LOCF)] by ADT. Change in sexual functioning from baseline to Week 52 (LOCF) was assessed using the Massachusetts General Hospital Sexual Functioning Inventory (MGH-SFI), which consists of five items: interest in sex, sexual arousal, achievement of orgasm, erection maintenance and sexual satisfaction with lower scores indicating better sexual functioning. A sixth SFI item captures the overall improvement score since the last medication change on a scale of one to six, with six being much worse, one very much improved, and four unchanged.

Results: Overall mean change in CGI-S (n=285) by Week 52 was -1.5. Baseline CGI-S scores ranged from 4.2 to 4.4 for the individual ADTs. Mean change from baseline in CGI-S score by individual ADT were: escitalopram (n=64) -1.5, venlafaxine XL (n=48) -1.4, sertraline (n=39) -1.7, fluoxetine (n=41) -1.3, paroxetine or CR (n=37) -1.5, bupropion XL or SR (n=46) -1.4, duloxetine (n=71) -1.7 and mirtazapine (n=3) -1.3. Pooled data from all ADTs showed that improvement on the five SFI items (n=155) ranged from -0.2 (sexual satisfaction) to -0.6 (for both interest in sex and orgasm). The mean overall improvement score of 3.8 indicated unchanged to minimally improved sexual function. There were no unexpected treatment emergent adverse effects with the long-term use of adjunctive aripiprazole with various ADTs.

Conclusions: Adjunctive aripiprazole improved CGI-S scores to a similar degree when added to different classes of ADT. Sexual functioning in patients on antidepressants also was modestly improved after addition of aripiprazole to the ADT. The lack of deterioration in sexual functioning in patients treated long-term with adjunctive aripiprazole is important new information for clinicians making treatment decisions about adjunctive therapy for patients with MDD.

Source of Funding: Bristol-Myers Squibb, Otsuka Pharmaceutical Co., Ltd.

Literature References:
Tuesday, June 15

Session I–53

Efficacy of Adjunctive Aripiprazole in Major Depressive Disorder (MDD) Patients with Minimal or Partial Response to Antidepressant Monotherapy

J. Craig Nelson, M.D.,1 Michael E. Thase, M.D.,2 Elizabeth E. Belloccchio, Ph.D.,3 Ross A. Baker, Ph.D. M.B.A.,1 Linda M. Rollin, Ph.D.,1 Robert D. McQuade, Ph.D.,1 Ronald N. Marcus, M.D.,2 Robert M. Berman, M.D.4

1University of California, San Francisco, 2University of Pennsylvania School of Medicine, Pittsburgh, 3Bristol-Myers Squibb, Plainsboro, NJ, 4Bristol-Myers Squibb, Wallingford, CT, 5Otsuka Pharmaceutical, Development and Commercialization, Inc., Princeton, NJ

Background: Augmentation strategies have been employed in major depressive disorder (MDD) patients with partial response to antidepressant therapy (ADT), while patients with minimal response are often switched to another ADT.

Methods: Data from three similar studies1–3 were performed to assess the efficacy of adjunctive aripiprazole (Adj ARI) versus adjunctive placebo (Adj PBO) in MDD patients with minimal and partial response to ADT monotherapy. In this analysis, minimal responders were defined as patients having ≤25% improvement on the Montgomery Åsberg Depression Rating Scale (MADRS) total score during the prospective ADT monotherapy phase; partial responders had 25–49% improvement. Change over time on the MADRS, response (≥50% reduction in MADRS), and remission (MADRS<10 and ≥50% reduction), was examined in the adjunctive treatment phase using analysis of covariance (ANCOVA) and Cochran–Mantel–Haenszel (CMH) tests with last observation carried forward (LOCF).

Results: Endpoint (LOCF) data are presented in the table.

<table>
<thead>
<tr>
<th>MINIMAL RESPONDERS</th>
<th>PARTIAL RESPONDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>72% (748/1041)</td>
<td>28% (293/1041)</td>
</tr>
<tr>
<td>Adj ARI</td>
<td>Adj ARI</td>
</tr>
<tr>
<td>28.8 (389)</td>
<td>28.6 (357)</td>
</tr>
<tr>
<td>Adj PBO</td>
<td>Adj PBO</td>
</tr>
<tr>
<td>21.1 (122)</td>
<td>21.1 (127)</td>
</tr>
<tr>
<td>CHANGE FROM BASELINE MADRS</td>
<td></td>
</tr>
<tr>
<td>6.49</td>
<td>6.09</td>
</tr>
<tr>
<td>RESPONSE RATE</td>
<td>RESPONSE RISK RATIO VERSUS PBO</td>
</tr>
<tr>
<td>19% (72/389)</td>
<td>1.90</td>
</tr>
<tr>
<td>36% (122/337)</td>
<td>1.23</td>
</tr>
<tr>
<td>RESPONSE RISK RATIO VERSUS PBO</td>
<td></td>
</tr>
<tr>
<td>1.90</td>
<td>1.23</td>
</tr>
<tr>
<td>REMISSION RATE (%)</td>
<td>REMISSION RISK RATIO VERSUS PBO</td>
</tr>
<tr>
<td>12% (45/389)</td>
<td>2.00</td>
</tr>
<tr>
<td>24% (86/357)</td>
<td>1.30</td>
</tr>
<tr>
<td>REMISSION RISK RATIO VERSUS PBO</td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td>1.30</td>
</tr>
<tr>
<td>31% (39/125)</td>
<td>8</td>
</tr>
<tr>
<td>41% (68/167)</td>
<td>11</td>
</tr>
<tr>
<td>49% (69/141)</td>
<td>7</td>
</tr>
</tbody>
</table>

Response rates with adjunctive aripiprazole were significantly higher than adjunctive placebo as early as Week 9, one week after treatment initiation, for both ADT minimal (6% versus 3%; p<0.05) and ADT partial responders (8% versus 2%; p<0.05). Remission rates were significantly higher in the adjunctive aripiprazole group, starting at Week 10, for both ADT minimal (3% versus 1%, p<0.05) and ADT partial responders (5% versus 2%, p<0.05). Adverse events occurring at a rate of ≥5% and twice the placebo rate were akathisia, dizziness, somnolence, restlessness, insomnia, constipation, fatigue and blurred vision.

Conclusions: Adjunctive aripiprazole showed significant benefit over ADT monotherapy in minimal responders, as confirmed by a number needed to treat (NNT) of six for response and eight for remission. The overall benefit was less consistent in partial responders (NNT of 12 for response and 11 for remission); patients in both treatment groups continued to improve over time. In both the ADT minimal and ADT partial responders, the benefit of adjunctive aripiprazole was evident as early as one or two weeks of treatment. Aripiprazole was well-tolerated.

Source of Funding: Bristol-Myers Squibb, Otsuka Pharmaceutical Co., Ltd.

Literature References:

Session I–54

Effect of a 12-Week Exercise Program on Serum Brain Derived Neurotrophic Factor (BDNF) in Major Depressive Disorder (MDD)

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Objective/Hypothesis: Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin that appears to have an important role in mental illness. BDNF in the serum of subjects with major depressive disorder (MDD) is lower than that of controls and corrects with medication treatment. However, the effect of BDNF in a different clinical treatment strategy is less known. In this study, exercise is emerging as a valuable treatment for MDD because it is low cost, cannot interact with medications and has general health benefits. In addition, there is extensive literature showing that exercise effects central BDNF production and mood behaviors in animal models of MDD. The primary aim of this study is to determine if exercise, measured in calories expended per week over 12 weeks, has an effect on serum BDNF in subjects with depression. We hypothesize that greater caloric expenditure will be associated with greater increase in serum BDNF level. The secondary aim is to show that this change in BDNF correlates with change in depression severity, as measured by the Inventory of Depressive Symptomatology, Clinician Rated Version (IDS-C). Based on existing serum BDNF literature in human subjects, we expect that increase in BDNF will correlate with clinical improvement.

Method/Proposed Methods: The Treatment with Exercise Augmentation for Depression (TREAD) study is a randomized trial which examined the use of exercise as an adjunctive treatment for MDD in subjects who had partial response to an adequate trial of a selective serotonin reuptake inhibitor (SSRI). As part of this study, 79 subjects provided blood samples at baseline and 12 weeks for serum BDNF measurement. Blood samples will be analyzed using an enzyme-linked immunosorbent assay (ELISA). Subjects were assessed weekly with the IDS-C, which was the primary outcome measure for TREAD during the trial. The samples have begun processing and the data should be obtained and analyzed over the next few months. We will use a correlation analysis to examine the relationship between energy expenditure and change in BDNF. This will be done in the entire group and in the high and low dose groups separately because it is possible, within a group that has a baseline BDNF of MDD the capacity for exercise may change over time. For the secondary aim, a similar analysis of correlation between change in BDNF and clinical improvement will be performed. Because age and sex may play a role in BDNF levels, they will be used as co-variants in the analysis.

Discussion/Significance: This study further elucidates the complex relationships among metabolism, BDNF and mood. In addition to expanding our knowledge of serum BDNF as a biomarker of MDD treatment in general, it may help explain the relationship between physical activity and mood, leading to improvement in the treatment.

Source of Funding: University Endowment Funds.

Literature References:
Session I–55

A Double-Blind, Placebo-Controlled Trial of Quetiapine for the Treatment of Mixed Hypomania in Bipolar II Disorder (BDII)

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1Veterans Affairs Palo Alto Health Care System, Stanford University School of Medicine, Palo Alto, CA; 2Stanford University School of Medicine, CA

Background: While the lifetime prevalence of DSM-IV defined bipolar disorder (BDI) is estimated at 1.1% or more, there are limited data to guide treatment of BDII, and virtually no studies on treatment of mixed hypomania. Patients with BDII experience similar levels of psychosocial disability as those with bipolar I disorder (BDI). Recent work demonstrates that depressive symptoms during hypomania are common, occurring in 76% of visits where hypomania was noted for BDII patients.

Methods: The study was a two-site, randomized, placebo-controlled, double-blind, eight-week investigation of adjunctive quetiapine (QTP) versus placebo (PBO) for the treatment of patients diagnosed with BDII experiencing mixed hypomania defined as scores of >12 on the Youth Mania Rating Scale (YMRS) and >15 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at two consecutive visits. Primary outcomes included reduction of symptoms on the YMRS (hypomania) and MADRS (depression). QTP or PBO was added to stable psychotropic regimens; and adjunctive use of lorazepam was allowed during the first two weeks.

Results: Fifty-five patients with BDII were randomized to receive either adjunctive QTP (n=30) or PBO (n=25). At study entry, mean MADRS total score was 28.11 (SD=7.5) and mean YMRS total score was 21.0 (SD=4.7). One site enrolled a greater proportion of females (87% versus 64%, p=0.049), and the PBO group reported more lifetime depressive episodes (4.2 versus 3.6, p=0.03). No other significant differences in baseline demographics or clinical characteristics were noted between sites or treatment groups. Thirty patients (54.5%) were not prescribed additional psychotropics, 17 were prescribed one additional psychotropic, seven were prescribed two, and one patient was prescribed three psychotropics during the study.

Using an intent-to-treat analysis, the QTP group showed significantly greater improvement in depressive symptoms (MADRS) (14 versus 7 point decrease; F=5.45 (df=1); p<0.05). For symptoms of hypomania (YMRS) there were no significant group differences in change over study duration (F=2.34 (df=1); p=0.132). There were few differences between groups in experience of side effects. Sedation was the most commonly reported side effect in the QTP group, with 16 (53.3%) reporting this side effect compared to 4 (16%) of the PBO group (x²=8.21 (df=1); p<0.05).

Conclusions: In this eight-week study, adjunctive quetiapine was associated with reduction in depressive symptoms in BDII patients experiencing mixed hypomania. Further analyses on effectiveness and side effects will be presented.

Source of Funding: AstraZeneca Pharmaceuticals (ISS 0333).

Literature References:

Session I–56

Double-Blind, Placebo-Controlled Efficacy and Safety Study of Lisdexamfetamine Dimesylate in Adolescents with Attention Deficit Hyperactivity Disorder (ADHD)

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1Center for Psychiatry and Behavioral Medicine, Las Vegas, NV; 2Florida Clinical Research Center, LLC, Bradenton; 3Shire Development Inc, Wayne, PA; 4University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH

Background: Lisdexamfetamine dimesylate (LDX, Vyvanse®, Shire U.S. Inc.) is a long-acting prodrug stimulant indicated for attention deficit hyperactivity disorder (ADHD) in children (six to 12 years) and adults, but not adolescents (13–17 years). LDX is endogenously converted to d-amphetamine. This study examines the efficacy and safety of LDX versus placebo in adolescents with ADHD.

Methods: Eligible subjects (13–17 years) with at least moderately symptomatic ADHD (ADHD Rating Scale IV: Clinician Version [ADHD-RS-IV] score ≥28) were randomized to placebo or LDX (30, 50 or 70 mg/d) with forced-dose titration in a four-week, double-blind study. Primary and secondary efficacy measures were the ADHD-RS-IV and Clinical Global Impression—Improvement (CGI-I) scale. Safety assessments included adverse events (AEs), vital signs, laboratory findings, physical exam and electrocardiogram (ECG).

Results: Overall, 314 subjects were randomized, 309 included in efficacy analyses, and 49 withdrew (11 due to AEs). At endpoint, changes in ADHD-RS-IV were significantly greater for each LDX dose versus placebo; least squares mean (SE) change was -12.8 (1.25), -18.3 (1.25), -21.1 (1.28) and -20.7 (1.25) for placebo, 30, 50 and 70 mg/d LDX (p<0.006 for all), respectively. Significant differences in ADHD-RS-IV scores relative to placebo were observed in each LDX group beginning at Week 1 and at each week throughout the study. The percentage of subjects rated very much or much improved at endpoint as measured by CGI-I was significantly greater for LDX (all doses) than for placebo (69.1% versus 39.5% [p=0.001]), respectively. The most frequently reported LDX treatment-emergent AEs (>5%) were decreased appetite, headache, insomnia, weight decrease and irritability. There were small mean increases in pulse and systolic and diastolic blood pressure with LDX. There were no clinically meaningful trends in ECG.

Conclusions: LDX was effective compared with placebo in decreasing ADHD symptoms from the first week of treatment in adolescents with ADHD. LDX demonstrated a safety profile consistent with previous LDX studies in children or adults.

Source of Funding: Shire Development, Inc.

Literature References:
Session I–57

**Electroconvulsive Therapy (ECT) Augmentation in Clozapine-Resistant Schizophrenia**

Georgios Petrides, M.D., Raphael J. Braga, M.D., Alan Mendelowitz, M.D., Samuel H. Balline, M.D., Nina Schoeller, Ph.D., Max Fink, M.D.

The Zucker Hillside Hospital, Northshore-Long Island Jewish Health System, NY

**Background:** Clozapine is indicated for the treatment of medication-resistant schizophrenia. Nonetheless, up to 70% of patients who tolerate an adequate trial of clozapine fail to benefit from it or respond partially. In a randomized, controlled, single blind, National Institute of Mental Health (NIMH)-sponsored study we evaluated the efficacy of electroconvulsive therapy (ECT) as an augmentation strategy for the treatment of clozapine-resistant schizophrenia.

**Methods:** Patients with schizophrenia on a stable dose of clozapine and serum levels >550 mcg/ml for at least eight weeks, with persistent psychotic symptoms (>12 in the Brief Psychiatric Rating Scale [BPRS] psychosis subscale) and no current mood symptoms were included. Patients were randomized to receive eight weeks of ECT in addition to clozapine or to continue with clozapine treatment for eight weeks. Patients in the pharmacotherapy arm, who did not respond after eight weeks, crossed over to the ECT arm and received the combination treatment for another eight weeks in an open trial. We report response rates at 20% and 40% reduction in the psychosis items of BPRS.

**Results:** Twenty patients were randomized to receive ECT+clozapine and 19 patients to continue clozapine pharmacotherapy. The mean age was 39.3 (sd=9.6). The mean BPRS rating was 46.0 (sd=9.6) and for the psychosis subscale was 16.5 (sd=3.7). Defining response as 20% reduction of the psychosis subscale, there were no responders in the pharmacotherapy group, compared to 12 of 20 (60%, p<0.001) in the ECT group. If we define response as 40% reduction, there were no responders in the pharmacotherapy group, compared to 10 of 20 (50%, p<0.001) in the ECT+clozapine group. In the open cross-over phase there were 11 of 15 (73.3%) responders to ECT+clozapine when response was defined as 20% reduction as the criterion and six of 15 (40%) when 40% was used. The combination of ECT and clozapine was well tolerated and no unusual side effects were observed.

**Conclusions:** These data suggest that the combination of clozapine and ECT is an effective treatment for patients with clozapine-resistant schizophrenia.

**Source of Funding:** National Institute of Mental Health (MH08163).

**Literature References:**

Session I–58

**Folate Supplementation in Schizophrenia**

Kelsey L. Shannahah, B.A.1, Michele Hill, M.B., MRCPsych1, Sarah C. Jasinski, B.A.2, Eric A. Macklin, Ph.D.1, Lisa H. Raeke, M.A.3, Joshua L. Roffman, M.D., Ph.D.2, Donald C. Goff, M.D.1

1Massachusetts General Hospital, Boston, 2Massachusetts General Hospital, Charlestown

**Objective:** We previously found that low serum folate concentrations and MTHFR C677T genotype interacted to predict negative symptom severity in patients with schizophrenia. This study was designed to assess the effect of folate supplementation on negative symptoms in relation to MTHFR genotype.

**Methods:** Stable adult schizophrenia outpatients with prominent negative symptoms (moderate or greater severity on at least one Scale for Assessment of Negative Symptoms [SANS] global assessment subscale) were randomized, double-blind, to folate two mg/d or matching placebo for a 12 week trial. The primary outcome measure was the modified SANS total score measured at baseline and Weeks 4, 8 and 12 using a mixed model analysis. Positive symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) and cognitive function with a battery comprised of the California Verbal Learning Test (CVLT), Stroop, Weschler Adult Intelligence Scale (WAIS-III); digit symbol coding, block design, arithmetic; Wisconsin Card Sorting Test (WCST), verbal fluency task (FS) and finger tapping. In addition, serum and RBC folate and plasma homocysteine concentrations were assayed and DNA genotyped for MTHFR C677T.

**Results:** Forty-six patients consented, 32 received study drug and 28 completed the trial. Serum and RBC folate concentrations significantly increased in subjects receiving folate supplementation, although changes in plasma homocysteine concentration did not differ significantly between treatment groups. Folate supplementation did not significantly affect negative symptoms, positive symptoms or the composite cognitive score compared to placebo in the full sample. However, there was a significant genotype x treatment effect on negative symptoms (p=0.01), with a trend for greater response with placebo in CCs (effect size 0.71; p=0.07) and a trend for greater response with folate in TTs and TCs (effect size 0.61; p=0.08). Among subjects who received folate, the difference in SANS 12-wk changes between MTHFR T- (n=9, delta=-9.4 units) and CC (n=8, delta=-5.8 units) was not significant (effect size 0.32).

**Conclusions:** We did not detect a therapeutic benefit of folate supplementation in a sample of patients with residual negative symptoms. A possible association between genotypes associated with reduced MTHFR activity and benefit from folate supplementation should be investigated further.

**Source of Funding:** NARSAD.

**Literature References:**
Session I–59

How to Assess the Speed of Antidepressant Effect: Insights from the Fixed Combination Pipamperone and Citalopram (PIPCIT) Clinical Trial Program

Kees Bol, Ph.D.¹, Ludo Haazen², Erik Buntinx², Michael Thase, M.D.³

¹Kinesis Pharma B.V., Breda, Netherlands, ²PharmaNeuroBoost, Alken, Belgium, ³University of Pennsylvania School of Medicine, Philadelphia

Background: Selective serotonin reuptake inhibitors and other antidepressants are thought to require six to eight weeks to achieve their full antidepressant effect. Accelerating this effect is considered to be a major medical need. However, there is no consensus on how to best assess speed of antidepressant effect. Pipamperone (Pip) is a novel second-generation neuroleptic that is under development with citalopram (CIT) as a fixed combination (PIPCIT). The highly selective SHT2A and D4 receptor blockade of low-dose Pip is thought to accelerate the antidepressant effect of CIT. In the PIPCIT Clinical Trial Program, the speed of effect of PIPCIT is assessed using newly developed endpoints.

Methods: In a randomized, double-blind phase II clinical trial, it was hypothesized that PIPCIT (10 and 40 mg) accelerates the anti-depressant effect of CIT (40 mg). Endpoints included the rate of early and sustained response (ESR; =50% reduction in total Montgomery-Asberg Depression Rating Scale (MADRS) score at Weeks 2 and 4) and, post hoc, the average TS50, defined as the time to reach 50% of the maximum decrease in total MADRS score based on nonlinear mixed-effect modelling.

Results: ESR was seen in 21% (n=17/80) of the PIPCIT patients versus 9% (n=6/67) of the CIT patients. In responders, mean (SE) TS50 was 24.6 (8.4) days in PIPCIT versus 29.4 (10.1) days in CIT.

Conclusions: Time to response appeared to be the most sensitive endpoint, whereas the rate of ESR can be considered more clinically relevant. Both endpoints are informative and complementary and should be of major interest in planned phase III PIPCIT studies.

Source of Funding: PharmaNeuroBoost NV.

Literature References:

Session I–60

A Pattern Recognition Matrix for Placebo-Response in Schizophrenia

Mark G.A. Opler, Ph.D., M.P.H.¹, Guillermo DiClemente, Ph.D., M.S.W.²

¹ProPhase LLC, NY, ²CROnos CCS, Jersey City, NJ

Background: Central nervous system (CNS) clinical trials present significant methodological and logistic challenges. High failure rates of Phase 2 and Phase 3 studies, weak signal detection, high placebo response rates and treatment by country interactions are common concerns. There is a need for real-time capability to detect inconsistencies in efficacy outcome measures and to predict individual-level or group-level placebo response. Training and calibration to improve inter-rater reliability is one method; it is widely reported in the literature that the more training raters receive during the course of a trial, the less rater drift is observed and the more likely a trial will not fail. Placebo response has been identified as a problem across indications, and it is reasonable to assume that even very high inter-rater reliability will be undermined if large numbers of placebo responders are enrolled in a trial.

Methods: A pattern recognition matrix for placebo-response in schizophrenia was developed based on a Phase II study of schizophrenia conducted in the U.S. A data monitoring algorithm based on the Positive and Negative Syndrome Scale (PANSS) was retrospectively applied to the unblinded data and score patterns for the placebo responders versus placebo non-responders were analyzed.

Results: A total of 35 placebo responders (those who completed all eight study visits) and 35 randomly selected placebo non-responders were compared. For certain score patterns during the first two visits, patients were significantly likely to be placebo responders. Within this sample of patients who were randomized to placebo, those who demonstrated the pattern within the initial study visits were approximately three times more likely (OR=2.9, p=0.027) to demonstrate a placebo response.

Conclusions: This initial finding suggests that this method could aid in the detection of placebo response early in a trial. In concert with a data-monitoring process we would expect more robust signal detection. The use of the same system, coupled with ongoing training, has demonstrated significant improvements in reliability, increasing the ICC by 19% in a three-month period. If deployed at startup, this method provides a cost-effective way of managing the data quality in RCTs.

Source of Funding: ProPhase LLC.

Literature References:
2. Kemp AS, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophr Bull 2008 Aug 22. [Epub ahead of print].
Session I–61

Cross-Cultural Comparisons of American and Japanese Clinical Raters on Patients with Major Depressive Disorder using the 17-Item Hamilton Rating Scale for Depression (HAM-D-17)

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1ProPhase LLC, NY, 2Wyeth Research, Collegeville, PA, 3Wyeth Research, Paris, France

Background: Where clinical trials are conducted internationally, it is imperative to attend to cultural influences on clinical assessment tools. Cross-cultural literature has consistently shown that the expression of distress differs across cultures.1 In a study looking at differences in Hamilton Rating Scale for Depression (HAM-D) scores in Japan, United States and Europe, Ohishi and Kamijima2 indicated that the items ‘depressed mood’ and ‘feelings of guilt’ were rated as less severe in the Japanese cohort. This suggests that expression of emotionality may be assessed differently across cultures and in this study we sought to further explore this dimension.

Methods: We examined the results from 54 American and 106 Japanese raters in a global trial for desvenlafaxine. For training, raters watched and rated two videos of HAMD interviews conducted in English, each with a depressed woman of Asian descent (Japanese subtitles were provided). The first video depicted a more severely depressed patient (Video 1); the second video was conducted with a moderately depressed patient (Video 2).

Results: In Video 1, we found no significant difference in the overall HAMD score between Japanese (M=22.88, SD=3.26) and American raters (M=23.35, SD=3.17), t(133)=0.81, p=0.416 (two-tailed). However, in Video 2, we found a significant difference in the overall HAMD scores for Japanese raters (M=17.17, SD=3.08) and American raters (M=18.13, SD=2.35), t(115)=2.00, p=0.05, though the magnitude of the difference in the means was small (r2=0.025). On insomnia-late, anxiety psychic, and insight items, Japanese clinicians rated both patients as more severe than American raters.

Conclusions: Our analyses suggest that there are differences in how American and Japanese raters evaluate symptom severities of identical patients. While American and Japanese raters may not rate severely depressed patients (Video 1) that differently from each other, there seems to be cultural influences on how they rate patients with moderate depression (Video 2). The assessment of severe symptomatology does not seem to be impacted by cultural differences. However, rating mild to moderate level of depression may pose more of a challenge and has implications for training as well as interpretation of results from trial conducted in these regions.

Source of Funding: ProPhase LLC.

Literature References:

Session I–62

Treating Perinatal Depression in Low-Income Adolescents: Results from a Pilot Feasibility Study of Culturally Relevant, Brief Interpersonal Psychotherapy

Sarah E. Bledsoe, Ph.D., M.Phil., M.S.W., Amy Sommer, M.S.W., Abby Zeveloff, M.P.H., Anne-Marie Olarte, B.A.

University of North Carolina, Chapel Hill

Background: Perinatal depression is strongly associated with enduring negative maternal, child and family outcomes that disproportionately affect low-income, adolescent mothers.1 Yet evidence to guide the treatment of perinatal depression in adolescents is severely limited and studies that account for the economic, cultural and developmental needs of the most vulnerable mothers are virtually nonexistent.2 To address this critical gap, we conducted a pilot study testing the feasibility of providing culturally relevant, interpersonal psychotherapy (IPT-CRB)3 to depressed, pregnant adolescents in public health perinatal care clinics.

Methods: For this case series study, 15 participants were recruited from two public prenatal care clinics. In order to be included participants had to be pregnant, between 14–20 years of age, and meet DSM-IV-TR criteria for major depression. Participants were excluded if they met criteria for psychotic disorders, current substance abuse/dependence, or if they reported severe intimate partner violence. Treatment consisted of an engagement interview4 and eight sessions of IPT-CRB. Depressive symptoms were measured pre- and post-treatment using the Edinburgh Postnatal Depression Scale (EPDS).5 A paired t-test was conducted to examine differences in baseline and post-treatment depressive symptoms. We hypothesized that participants would have significantly lower levels of depressive symptoms post-treatment.

Results: Seventy-one percent of recruited adolescents met inclusion criteria. All eligible participants entered the study and 94% are currently enrolled. Preliminary analyses on the ten participants who have completed IPT-CRB reveal 100% experienced a decrease in depressive symptoms. Participants experienced an average decrease in EPDS score of 8.2 points post-treatment with average post-treatment scores five points below the screening cut-point of 12.

<table>
<thead>
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<th></th>
<th>Mean EPDS</th>
<th>Standard Deviation</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>15.2</td>
<td>(2.3)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>7.0</td>
<td>(5.2)</td>
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</tr>
</tbody>
</table>

Conclusions: Successful recruitment and retention of depressed adolescent combined with initial findings that depressive symptoms decrease significantly post-treatment indicate IPT-CRB is a feasible and promising treatment for adolescent perinatal depression. Findings are limited by the lack of a control group. A pilot randomized controlled trial is planned to validate pilot study findings.

Source of Funding: National Institutes of Health (NIH-2674, NIH K12-HD001441); University of North Carolina (PhD Research Grant, ECHO Pilot Grant), University Research Council, Junior Faculty Development Award, and Armfield-Reeves Innovation Fund.

Literature References:
Session I–63

Genotypic and Phenotypic CYP2D6 Poor Metabolizer Status among Outpatients with Depression Treated with Venlafaxine Extended Release

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Background: The prevalence of the cytochrome P450 2D6 (CYP2D6) poor metabolizer (PM) genotype is 5% to 10% in the general population; the prevalence in patients treated for depression is unknown. Chronic administration of concomitant medications can inhibit CYP2D6 activity, converting the phenotype of an individual with a non-PM genotype to a PM phenotype. Comorbid conditions are common in patients with depression, increasing the likelihood of concomitant medication use. The objective of this study was to determine, in a clinical sample of depressed outpatients treated with venlafaxine extended release (Effexor XR®; VEN ER), the prevalence the CYP2D6 PM phenotype, based on plasma O-desmethylvenlafaxine (ODV) to VEN ratio (ODV/VEN), compared with the prevalence of the actual CYP2D6 PM genotype.

Methods: This was a multicenter, open-label single-visit study in adult patients (age=18 years) treated with VEN ER (37.5 to 225 mg/d) for up to eight weeks. A 15-ml blood sample for phenotype and CYP2D6 genotype determinations was drawn four to 12 hours after the patient’s last VEN ER dose. Plasma ODV and VEN concentrations were determined for each patient, and phenotype was assigned. PM status was defined as ODV/VEN <1 based on published data. CYP2D6 genotype was determined for each patient. Agreement between phenotype and CYP2D6 genotype classifications was assessed using McNemar’s test. All concomitant medications were allowed, except for desvenlafaxine (Pristiq®) or generic VEN ER.

Results: Both ODV/VEN ratio and genotype results were available for 900 patients. In this clinical sample of patients with depression treated with VEN ER, 243/900 (27%) patients were classified as phenotypic PMs based on ODV/VEN ratio, whereas 35/900 (3.9%) were classified as CYP2D6 genotypic PMs (McNemar’s test, p<0.0001). In all, 34/35 (97%) patients genotyped as CYP2D6 PMs had a PM phenotype, however 209/865 (24%) genotypic non-PM patients were also classified as phenotypic PMs. Genotypic CYP2D6 intermediate metabolizers (IMs) were more likely than extensive metabolizer (EMs) to be classified as the PM phenotype; 49/81 (60%) genotypic IMs had a PM phenotype compared with 159/746 (21%) genotypic EMs.

Conclusions: A significant percentage of patients with CYP2D6 non-PM genotype were converted to phenotypic PM status, which may affect the tolerability and efficacy of VEN ER for those patients. Phenotype conversion in this population may be due to the use of concomitant medications to treat comorbid conditions.

Source of Funding: Pfizer, Inc.

Literature References:

Session I–64

Lurasidone Pharmacokinetics: Assessment of Potential for Drug–Drug Interactions

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Objective: To evaluate the potential risk for drug-drug interactions (DDIs) of lurasidone, a novel antipsychotic under development for the treatment of schizophrenia.

Methods: Six studies were conducted in volunteers to evaluate potential pharmacokinetic (PK) interactions with single or multiple-dose lurasidone. The PK of lurasidone was evaluated when co-administered with potent or moderate CYP3A4 inhibitors (ketoconazole and diltiazem); with the CYP3A4 inducer rifampin; and with lithium. Plasma concentration changes in midazolam, a CYP3A4 substrate and in an oral contraceptive (Ortho Tri-Cyclen) were evaluated in the presence of lurasidone. The effect of lurasidone on digoxin, a P-gp substrate was also investigated.

Results: Concomitant administration of lurasidone and ketoconazole resulted in increased lurasidone AUC (9.3-fold) and Cmax (6.8-fold). Co-administration of lurasidone and diltiazem resulted in a modestly increased lurasidone AUC (2.1-fold) and Cmax (2.1-fold). Co-administration of lurasidone and rifampin resulted in decreased lurasidone AUC and Cmax of ~65%. Lurasidone (120 mg) at steady-state exhibited weak CYP3A inhibition with a marginal increase in midazolam exposure. Concomitant administration of lurasidone and Ortho Tri-Cyclen had no effect on concentrations of constituent drugs. No interaction was observed with lithium 600 mg two times per day dosing and steady state dosing of lurasidone: A minimal (2–13%) effect on digoxin AUC and Cmax was observed with lurasidone at steady state.

Conclusions: Lurasidone should be administered cautiously with ketoconazole or other potent inhibitors of cytochrome P450 3A4. Lurasidone metabolism is potentiated with strong inducers of CYP3A4. Lurasidone does not appear to inhibit or induce any of the metabolic pathways for synthetic estrogens or progesterones, and thus can be safely given with oral contraceptives. Lithium does not affect lurasidone PK and lurasidone does not affect the disposition of P-gp substrates such as digoxin.

Source of Funding: Dainippon Sumitomo Pharma.

Literature References:
Objective: To analyze the safety of lorazepam used as rescue therapy in three clinical trials assessing the efficacy and safety of inhaled loxapine for the treatment of agitation in patients with schizophrenia or bipolar disorder.

Methods: Each of the trials was randomized, double-blind and placebo-controlled. Loxapine was administered via inhalation using a system that delivers thermally generated drug aerosol with IV-like kinetics (Staccato®). Consenting male and female adults, who met DSM-IV criteria for schizophrenia or bipolar I disorder, and presented with a relevant degree of agitation at baseline, were enrolled in the studies (N=787). A total of 473 patients with schizophrenia and 314 patients with bipolar I disorder received a single inhalation of either 0 mg, 5 mg or 10 mg of loxapine in an in-clinic treatment facility. Lorazepam rescue was administered when needed after the study drug to 135 of the 787 patients. Safety assessments were based on spontaneously reported adverse events (AEs). Selected AE categories were (1) any AE; (2) nervous system (NS) AEs; (3) sedation; (4) sedation or somnolence; and (5) sedation or somnolence or dizziness. Odds ratios (OR) for lorazepam to placebo and 95% confidence intervals (CIs) were calculated for each AE category and for AE categories stratified by lorazepam rescue.

Results: Of the 524 patients receiving loxapine, 36.5% reported any AE and 20.2% reported an NS AE. Of the 263 patients receiving placebo, 37.3% reported any AE and 22.1% reported an NS AE. The ORs for the five selected AE categories ranged from 0.896 to 1.425 and none of the five CIs excluded one. When stratified by lorazepam rescue, the ORs for the AE categories ranged from 0.596 to 1.665 and none of the 10 CIs excluded one. For sedation and sedation or somnolence, the OR was numerically smaller for the lorazepam/loxapine group than for the group receiving loxapine alone (i.e., the AE category was less likely).

Conclusions: The AE profiles were similar in patients receiving loxapine plus lorazepam compared with patients receiving loxapine alone. AZ-004 can be used safely with lorazepam rescue in patients with schizophrenia or bipolar disorder.

Source of Funding: Alexza Pharmaceuticals.

Literature References:

Session I–66

Quantifying Rater Drift in an International Sample of Investigators Participating in Standardized Rater Training Events: Is Positive and Negative Syndrome Scale (PANSS) Reliability Maintained Over Time?

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ProPhase LLC, NY

Background: Most studies that employ psychometric instruments to measure change in pathology over time implement some form of training in order to address the ongoing integrity of ratings following initial training. Rater drift has long been understood to negatively impact trial results but to date there have been few studies that have sought to systematically quantify this. In this study we looked at training data for the Positive and Negative Syndrome Scale (PANSS) from several time points to determine if drift occurred in this sample and if it affects certain items or subscales more than others.

Methods: Raters participating in standardized training scored the PANSS based on a video-taped interview. Data from the initial training session was compared to that obtained during a “refresher” session eight months later to determine if drift had occurred. Inter-rater reliability was obtained by the use of the intra-class correlation coefficient and compared at the two time points. Concordance with gold standard ratings was also compared for the same time points.

Results: Intra-class correlation coefficients (ICC) for raters (n=96) following initial training were in the good range at ICC =0.868 (p<0.001) and concordance with gold standard rating was high. At the eight month refresher training session reliability had fallen to ICC =0.738 (p<0.001) with gold standard concordance only in the moderate range. Positive, negative and general subscale reliabilities feel proportionally and observed/subjective items were most susceptible to decrease in reliability.

Conclusions: In this sample we found that over an eight month period rater drift did appear to occur as gauged by the metrics of reliability and concordance. This tendency to produce idiosyncratic or incorrect ratings seemed most prevalent in those items that were observed or subjective. Because this drift introduces random error into the data and this can have implications for sample size and power, it is imperative that standardized rater training at regular intervals occur.

Source of Funding: ProPhase LLC.

Literature References:
Session I–67

Reporting Adverse Event Data from Clinical Trials of Antipsychotic Agents
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2Ortho-McNeil Janssen, Scientific Affairs, LLC, Titusville, NJ

Background: Establishing safety profiles of new pharmaceuticals is a critical element of their development. However, most formal safety data presentations have significant limitations. This analysis evaluated relative risk (RR) of individual adverse events (AEs) for antipsychotic treatment compared with placebo from clinical trial databases to confirm, further explore and identify safety signals.

Methods: Three databases from randomized double-blind placebo-controlled studies of oral paliperidone extended release (ER) or injectable paliperidone palmitate (PP) were identified that used dosing similar to current product labels: one 13-week PP study (initiation dose 234 mg Day 1 and 39, 156 or 234 mg Day 8, followed by once-monthly injections) in schizophrenia (analysis 1); two six-week paliperidone ER studies (3–12 mg/day) in schizophrenia (analysis 2); and two six-week paliperidone ER studies (6–12 mg/day) in schizoaffective disorder (analysis 3). AE incidence rates were evaluated using graphical displays including RR and corresponding 95% CI. The primary goal was to highlight potential signals by providing estimates (and their precision) of treatment effect. RR with active treatment versus placebo was considered potentially significant when 95% CI did not cross one on the x-axis. No computations were adjusted for multiplicity.

Results: Graphical displays were generated for rates and RRs of the most common AEs for each database (≥5%, either group). Data suggested a potential higher risk with active treatment versus placebo for extrapyramidal disorder (RR=2.53; 95%CI=1.21,2.72) and tachycardia (RR=2.14; 95%CI=1.11,4.14) in analysis 2; and tremor (RR=2.33; 95%CI=1.05,5.18) in analysis 3. When 95% CIs for RR included one, risk was not considered significant between groups. However, borderline RRs greater with active treatment may be of clinical interest. AEs with a higher, though nonsignificant, risk with active treatment were injection site pain (RR=2.07; 95%CI=0.891,4.821) in analysis 1; akathisia (RR=1.74; 95%CI=0.99,3.05) in analysis 2; and hypertonia (RR=2.77; 95%CI=0.97,7.89), somnolence (RR=2.65; 95%CI=0.92,7.58), and dyspepsia (RR=2.21; 95%CI=0.85,5.74) in analysis 3.

Conclusions: RR (versus placebo) and AE rates were generated in graphical displays versus descriptive statistics for paliperidone ER and PP. The identified AEs may warrant greater attention by the clinician because the RRs provide additional information over aggregate summaries of patient data. This methodology may provide a clinically more interpretable way to report AE data from clinical trials.

Source of Funding: Ortho-McNeil Janssen Scientific Affairs, LLC.

Literature References:

Session I–68

Centralized Quality Control and Calibration (CQC): A New Method for Improving Assessment Quality and Scoring Accuracy in Clinical Trials
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Background: Central nervous system (CNS) clinical trials fail more often than their a priori powering indicates they should. Quality assurance/quality control (QA/QC) safeguards for clinical (including primary) outcome measures have rarely been utilized. By virtue of the number of raters performing assessments in large multisite trials the possibility of variability in ratings is increased. Rater drift over time is well-documented and common1 and superior interview performance as measured by the Rater Applied Performance Scale (RAPS) is associated with drug placebo separation.2 We report the first findings using Centralized Quality Control and Calibration (CQC), a new approach to monitoring and remediating the administration and scoring of clinical primary outcome measures.

Methods: Seventeen Calibrated Quality Reviewers were rigorously trained and continuously calibrated on scale scoring and interview quality. This cohort was tightly calibrated on the Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Anxiety (HAMA) and Hamilton Rating Scale for Depression (HAMD). ICCs =0.91–0.93. Data from multiple on-going clinical trials were pooled. One hundred-thirty-one site raters audio recorded all MADRS, HAMA or HAMD administrations and uploaded the audio files to a central server. A priori criteria for scoring accuracy and RAPS interview quality were established. Calibrated Quality Reviewers independently scored 492 site raters assessments and rated interview quality using the RAPS. Only after scores and RAPS were submitted was the Calibrated Quality Reviewer given access to the site raters’ scores. Feedback was provided to the site rater on both interview quality and scoring accuracy before their next reviewed assessment.

Results: Four hundred-ninety-two assessments have been reviewed to date. At the first review completed for 110 site raters, 51% met the a priori criteria for scoring accuracy and 60% for interview quality; 35% met both. By review six or later (n=55) there were substantial improvements: 69% met criteria for scoring accuracy and 87% for interview quality; 65% met both. Further analysis of RAPS domains showed that adherence and follow-up difficulties were the most common causes for not meeting interview quality criteria.

Conclusions: QA/QC of clinical assessments identified significant scale administration and scoring issues. Repeated feedback improved rater performance substantially. Study outcomes will be evaluated to determine the degree to which continuous QA/QC of study assessments mitigate risk of CNS trial failures.

Source of Funding: MedAvante, Inc.

Literature References:
Session I–69

Placebo Response in Trials of Antidepressants in Patients with Major Depressive Disorder

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Pfizer, Inc., Collegeville, PA

Background: The degree of placebo response provides a pivotal context for defining antidepressant efficacy in clinical trials. Evidence suggests an increase in the placebo response in the past decades. A variety of factors such as baseline severity of symptoms and attention paid to subjects during clinical trials have been proposed as explanations. The objective of this analysis is to examine the placebo response in Wyeth-sponsored antidepressant trials and was to explore factors that may be associated with changes in placebo response.

Methods: The analysis included data from all Wyeth-sponsored, randomized, double-blind placebo-controlled studies of venlafaxine and desvenlafaxine completed as of August 2009 involving adult patients with Diagnostic and Statistical Manual of Mental Disorders (DSM) defined major depressive disorder (MDD). Data from 22 studies in which patients received venlafaxine (25 to 375 mg/d) or placebo for up to eight weeks and from nine studies in which patients received desvenlafaxine (50 to 400 mg/d) or placebo for up to eight weeks were summarized. Effect sizes (using Cohen’s d) were calculated based on the 17-item Hamilton Rating Scale for Depression (HAM-D17) total score. Effect sizes were plotted against study start date, mean baseline HAM-D score, minimum baseline HAM-D score, and mean number of assessments per visit.

Results: In venlafaxine and desvenlafaxine studies, effect sizes generally decreased over time, suggesting an increase in placebo response. Mean baseline HAM-D17 scores did not appear to substantially influence effect size, although effect sizes tended to be lower as minimum baseline HAM-D17 scores increased. The mean number of assessments per visit increased over time. Effect sizes tended to decrease as the number of assessments per visit increased.

Conclusions: Further investigation and analysis of these and other factors that may influence placebo response in antidepressant studies is necessary. Future studies of antidepressants should be designed with such factors in mind. The demonstration of the efficacy of novel medications with potential antidepressant efficacy is jeopardized by the increase in placebo response in clinical trials.

Source of Funding: Pfizer, Inc.

Literature References:

Session I–70

Relationship between Probability of Receiving Placebo and Probability of Prematurely Discontinuing Treatment in Double-Blind, Randomized Clinical Trials for Major Depressive Disorder (MDD): A Meta-Analysis

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Objective: In double-blind, randomized placebo-controlled clinical trials for major depressive disorder (MDD), a greater likelihood of receiving placebo predicts greater antidepressant-placebo “separation,” a direct measure of the success of a clinical trial. However, patients who are less likely to receive active therapy (and more likely to receive placebo) may be at increased risk of attrition which, in turn, can limit the statistical power of a study as well as the generalizability of the study results (since only a fraction of the studied population was exposed to treatment). Our aim in the present analysis was to investigate whether the probability of prematurely discontinuing treatment is influenced by the probability of receiving placebo versus active treatment in double-blind, randomized placebo-controlled clinical trials for MDD. A secondary aim was to examine whether discontinuation rates predicted clinical trial outcome.

Methods: Medline/Pubmed publication databases were searched for randomized, double-blind placebo-controlled trials of antidepressants for adults with MDD. The search was limited to articles published between January 1, 1980, and September 9, 2008 (inclusive). 1980 was used as a cut-off in our search in order to decrease diagnostic variability, since the DSM-III was introduced in 1980. In order to expand our database, we then reviewed the reference list of all studies identified with Pubmed/Medline.

Results: One hundred-sixty-nine manuscripts involving 247 drug-placebo comparison were pooled (n=36,603). Pooled discontinuation rates for drug and placebo were 31.4% versus 33.2%. A meta-regression established that the likelihood of receiving placebo did not predict either antidepressant discontinuation rates, placebo discontinuation rates or the risk ratio of discontinuing antidepressants versus placebo. The probability of discontinuation was not found to influence the relative likelihood of responding to antidepressant versus placebo (the estimate of the treatment effect).

Conclusions: In the present work an increased likelihood of receiving placebo did not inflate study discontinuation rates which, in turn, did not influence the degree of antidepressant-placebo “separation.” Therefore, decreasing the probability of receiving active therapy may be an effective approach to improve the likelihood of success in placebo-controlled clinical trials without leading to increased discontinuation rates that would result in a decrease in statistical power.

Source of Funding: None.

Literature References:
The MedAvante Analysis of Rating Quality-Alzheimer’s Disease (MARQ-AD): A New Measure of Interview Quality in Alzheimer’s Disease Trials

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Cognitive assessments as currently administered by clinicians in pharmaceutical trials of Alzheimer’s disease (AD) present many challenges. Across trials, both structured and semi-structured assessments are plagued by administration and scoring variability. Inter-rater reliability can be compromised by administration and scoring deviations, or when clinical judgment is required to resolve ambiguous instructions or scoring guidelines. Taken together, this variability in outcome measures can undermine a true treatment effect.

The challenges of standardized administration and scoring of AD assessments such as the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) have been documented. Even experienced raters working on multiple dementia protocols have a significant likelihood of administration/scoring inconsistency, which decreases signal detection. Furthermore, long trials incur increased rater turnover that can exacerbate these standardization issues. The industry commonly reports problems with structured and unstructured scales, although the extent of the problems has not been well-documented. We present a new instrument designed to characterize and monitor variability in the administration of these types of scales.

The MedAvante Analysis of Rating Quality-Alzheimer’s Disease (MARQ-AD) was developed to quantify critical domains of rater performance and address reasons for administration and scoring variability encountered in AD assessments. The MARQ-AD was designed as a tool to assess raters’ clinical interview skills, both as a clinical trial qualification and as an ongoing performance assessment tool. This methodology has been shown to be effective in other disease states that utilize subjective assessment instruments. This poster presents the new MARQ-AD and its scoring guidelines. The benefit to AD and other dementia clinical trials is improved interview standardization and quality, resulting in decreased rater drift and ratings variability.

Source of Funding: MedAvante, Inc.

Literature References:

Session I–72

Variables Associated with Medication Satisfaction in Patients with Schizophrenia

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Background: Medication satisfaction is an important outcome for the treatment of schizophrenia. However, to our knowledge, predictors of satisfaction have not been clearly identified or distinguished across treatments. This analysis examined variables correlated with medication satisfaction with paliperidone extended release (ER) versus risperidone.

Methods: Data were from two similar double-blind, placebo-controlled trials in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization (NCT00334126, NCT00061802). Study 1 examined risperidone treatment and study 2 examined paliperidone ER treatment; both included quetiapine arms. Analyses focused on satisfaction with active treatments during monotherapy (Week 2 endpoint). Satisfaction with quetiapine was used to compare findings across studies. Variables: Medication Satisfaction Questionnaire (MSQ; 1=extremely dissatisfied to 7=extremely satisfied), Clinical Global Impressions Scale for Schizophrenia (CGI-S), Positive and Negative Syndrome Scale (PANSS), Brief Adherence Rating Scale (BARS), and Simpson-August Rating Scale (SAS) scores, and prolactin levels. Spearman correlation coefficients were calculated.

Results: Mean (SE) medication satisfaction questionnaire (MSQ) scores were similar across studies at Week 2 endpoint: 5.2 (0.1), risperidone; 4.9 (0.1), paliperidone ER; 4.7 (0.1) in study 1 and 4.5 (0.1) in study 2 for quetiapine. CGI-S change scores showed the highest (though moderate) correlations with MSQ, regardless of treatment: 0.517, risperidone; 0.466, paliperidone ER (quetiapine: 0.213 [study 1], 0.438 [study 2]). PANSS total change scores correlated moderately with MSQ: 0.446, risperidone; 0.327, paliperidone ER (quetiapine: 0.508 [study 1], 0.387 [study 2]). Correlation coefficients between PANSS positive factor change scores and MSQ were 0.467 for risperidone and 0.260 for paliperidone ER (quetiapine: 0.316 [study 1]; 0.321 [study 2]). Correlation for PANSS excitement/uncontrolled hostility factor change scores were 0.382 for risperidone and 0.296 for paliperidone ER (quetiapine: 0.430 [study 1]; 0.449 [study 2]). Correlations for other factor score changes for risperidone and paliperidone ER were low (0.152–0.264). MSQ was poorly correlated with BARS and SAS scores and prolactin level changes for all groups (-0.051 to 0.142).

Conclusions: Findings suggested that changes in overall clinical impression and symptoms were moderately correlated with medication satisfaction, regardless of treatment. Correlation of medication satisfaction with symptom improvement was driven largely by improvement in positive symptoms for risperidone-treated patients. Corresponding correlations for paliperidone ER were weaker. Because MSQ scores were similar across treatment arms in the two studies, improvement in variables other than positive symptoms may be driving satisfaction with paliperidone ER.

Source of Funding: Ortho-McNeil Janssen, Scientific Affairs, LLC.

Literature References:
Session I–73

The Efficacy and Safety of the Novel Antipsychotic Cariprazine in Acute Exacerbation of Schizophrenia

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Objective: To evaluate the safety and efficacy of cariprazine, a D3/D2 antagonist-agonist partial agonist with preference for the D3 receptor, in acute exacerbation of schizophrenia.

Methods: International, double-blind, placebo-controlled, fixed-dose trial in patients (18–60 years) with DSM-IV-defined schizophrenia, current psychotic episode <2 weeks, and Positive and Negative Syndrome Scale (PANSS) total score ≥80 and ≤120. After one-week washout, patients were randomized to six-week double-blind treatment (cariprazine 1.5, 3.0, or 4.5 mg/d; risperidone 4.0 mg/d; or placebo); a two-week safety period followed. Primary and secondary efficacy: change from baseline to Week 6 (last observation carried forward [LOCF]) in PANSS total score and Clinical Global Impressions-Severity (CGI-S) score, respectively. Safety: adverse events (AEs), vital signs, laboratory measures and extrapyramidal symptom scale (EPS).

Results: Of 732 randomized patients, 64% completed the study. Mean baseline PANSS (96.7–98.1) and CGI-S scores (4.7–4.9) were similar between groups. Improvement in PANSS total score at Week 6 was greater for cariprazine 1.5, 3.0 and 4.5 mg/d versus placebo (p<0.001; LOCF); placebo-adjusted improvements were −7.5, −8.9, −10.4, respectively. Statistically significant improvements were observed for each cariprazine group relative to placebo in CGI-S, PANSS Positive subscale scores (1.5 mg/kg/day, p=0.0057; 3.0 and 4.5 mg/kg/day, p<0.0001) and PANSS Negative subscales scores (p<0.0001 all doses). Statistically significant differences (p<0.0001) were also noted for risperidone versus placebo in PANSS total score, CGI-S and PANSS subscales. The most common AEs in the cariprazine groups were insomnia, EPS, akathisia, sedation, nausea, dizziness and constipation; AE incidence was not dose proportional. Discontinuation due to AEs was 15% for placebo, 10%, 5% and 8% for cariprazine 1.5, 3.0 and 4.5 mg/d, respectively, and 9% for risperidone 4.0 mg/d. EPS-related AE incidence was 13% for placebo, 21%, 22%, 22% for cariprazine 1.5, 3.0 and 4.5 mg/d, respectively, and 29% for risperidone 4.0 mg/d. Potentially clinically significant weight increase (>7%) was more pronounced for risperidone (16.7%) than cariprazine (8.5%, 10.7%, 4.9% for 1.5, 3.0 and 4.5 mg/d, respectively) or placebo (2%). There were no clinically meaningful metabolic parameter changes for cariprazine; no prolactin elevation or QTc prolongation was observed.

Conclusions: Cariprazine significantly improved PANSS and CGI-S scores versus placebo in patients with acute exacerbation of schizophrenia and was generally well tolerated.

Source of Funding: Forest Laboratories, Inc., Gedeon Richter, Ptc.

Literature References:

Session I–74

Depressed Adolescents Treated with Exercise (DATE): Exercise versus Stretch-Controlled Randomized Trial

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1University of Texas, Southwestern Medical Center, Dallas, 2Cooper Institute, Dallas, TX

Background: Exercise treatment for depressed adults has been found to be effective.1 The objective of the present study was to extend the adult findings to unmedicated depressed adolescents and to determine if (1) they will adhere to an exercise only intervention, and (2), if they are likely to benefit.

Methods: Non-medicated outpatient adolescents with major depressive disorder, age 12–17, were enrolled in a National Institute of Mental Health (NIMH)-funded study of depressed youth treated with exercise.2 Each adolescent completed a two-week diagnostic evaluation to determine study eligibility. Enrollment required consensus diagnosis of major depressive disorder (MDD) based on the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL), with Children’s Depression Rating Scale Revised (CDRS-R) >40 and Clinical Global Impressions Scale (CGI-S) Severity >4 and no medical illnesses that would prevent participation in physical activity. A feasibility trial of 10 eligible patients were randomized to receive 12 weeks acute treatment of either aerobic exercise (12 kcal/kg; n=6) or stretch routines (<4 kcal/kg; n=4), with periodic assessment on all study measures. All subjects were monitored on a 24hr/7day basis with Actical accelerometry to determine total activity, kcal energy expenditure, and adherence.

Results: Based on repeated measures of weekly Quick Interview of Depression Symptoms—Self-Rated (QIDS-SR) and blinded tri-weekly CDRS, QIDS-C Clinician rated, and CGI-improvement ratings, responders to both exercise and stretch showed significant reduction in depression scores. After 12 weeks, 8/10 were responders (CGI-I <2, and CDRS-R score <28 or a greater than 50% reduction from baseline). There was both a significant increase in total activity for both groups and kcal energy expenditure (greater energy expenditure in the exercise group than the stretch group) that was inversely related to the reduced CDRS depression scores. Importantly, this feasibility study demonstrated that depressed adolescents will adhere to either an exercise or stretch routine protocol for up to three months that does lead to significant reduction in overall depression symptoms.

Conclusions: Results suggest that an ongoing exercise treatment regime (either aerobic exercise or a series of stretching routines) for adolescents is feasible, potentially effective and may prove to be an additional useful therapeutic alternative or adjunct to antidepressant medication for pediatric depression.


Literature References:
Session I–75

Levomilnacipran in the Treatment of Major Depressive Disorder: Analysis of Efficacy across Symptoms

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Background: Levomilnacipran, the (1S, 2R) enantiomer of milnacipran, is a selective and potent norepinephrine and serotonin reuptake inhibitor in clinical development for the treatment of major depressive disorder (MDD). The efficacy and safety of sustained release levomilnacipran was evaluated in a placebo-controlled clinical trial.

Methods: In a 10-week, randomized, flexible-dose, international study, patients (18–70 years) with DSM-IV-defined MDD received levomilnacipran 75–100 mg/day (n=276) or placebo (n=277). All outcomes were analyzed for change from baseline to Week 10 for levomilnacipran versus placebo using mixed-effects model repeated measures (MMRM) on the full analysis set (FAS). Primary efficacy variable was the Montgomery-Åsberg Depression Rating Scale (MADRS) score. Secondary and additional efficacy variables included Hamilton Rating Scale for Depression–17-item (HAM-D-17) total score, Maier subscale score (core symptoms), HAMD-17 qualitative factor scores and the Sheehan Disability Scale (SDS) total and subscale (work, social life and family life) scores. Post hoc analyses evaluated changes in MADRS and HAMD-17 single items (MMRM analysis, FAS).

Results: Levomilnacipran treatment resulted in significantly greater improvement in change from baseline to Week 10 in both MADRS and HAMD-17 total score (p<0.0001). Levomilnacipran also showed significantly greater improvements relative to placebo for the Maier subscale (p<0.0001) and several key HAMD-17 qualitative factor scores including anxiety-somatization (p<0.001), retardation (p<0.001), and sleep (p<0.0003). Single-item analyses showed that levomilnacipran was superior to placebo on every MADRS item (p<0.01) and most HAMD-17 items, including early, middle and late insomnia (p=0.0004, p=0.0062, and p=0.015, respectively), work/activities (p<0.0001), psychomotor retardation (p<0.0066), general somatic symptoms (p<0.0001) and psychic anxiety (p=0.0009). Significantly greater improvements for levomilnacipran were also seen on SDS total and all subscale (work, social life, and family life) scores (p<0.0001). Discontinuation due to adverse events (AEs) occurred in 6.5% of placebo and 9.4% of levomilnacipran patients. Common treatment-emergent adverse events for levomilnacipran (>5% and at least twice the rate of placebo) were hyperhidrosis, constipation, tachycardia, palpitations, diarrhea and hypertension.

Conclusions: Levomilnacipran treatment resulted in significant improvement of both core and qualitative symptoms of depression as well as functional improvements (work, social life and family life). Levomilnacipran was well tolerated overall and showed robust efficacy across key symptoms of MDD.

Source of Funding: Forest Research Institute, Inc. and Pierre-Fabre Medicament.

Literature References:
Stahl SM, et al. SNRIs: Their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectr 2005;10(9):732–47.

Session I–76

Depressive Symptoms and Tobacco Use Predict Alcohol Outcome in Comorbid Depression and Alcoholism

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Background: Cigarette smoking and nicotine dependence and major depression are highly prevalent among patients with alcohol dependence. The impact of these symptoms on alcohol use outcomes have been less studied. We hypothesized that both cigarette smoking and depressive symptoms would predict alcohol use in patients with comorbid major depression (MD) and alcohol dependence (AD).

Methods: We examined whether the severity of depressive symptoms and of weekly cigarette smoking predict alcohol use outcomes in a sample of 80 subjects (46% females) with DSM-IV/Psychiatric Research Interview for Substance and Mental Disorders (PRISIM) comorbid diagnoses of MD and AD who completed a clinical trial evaluating the efficacy of fluoxetine (dose range 20–60 mg/day) +/- naltrexone (dose 50 mg/day). Patients were assessed weekly with the 17-item Hamilton Rating Scale for Depression (HAM-D-17), the Addiction Severity Index (ASI), and the Timeline Followback for alcohol use and for tobacco use.

Results: The mixed model with restricted maximum likelihood procedure and unrestricted covariance matrix was used. We examined whether the severity of depressive symptoms and of weekly cigarette smoking predict alcohol use outcomes at each assessment point, controlling for age, gender, socio-economic status, treatment group and time of assessments. The results of this study showed that cigarette smoking significantly predicted alcohol outcomes including weekly alcohol use (p<0.05), proportion of any drinking days (p<0.05) and proportion of heavy drinking days (p<0.05). Depressive symptoms strongly predicted weekly alcohol use (p<0.0001), proportion of any drinking days (p<0.01) and proportion of heavy drinking days (p<0.01).

Conclusions: The results of this study suggest that both cigarette smoking and depressive symptoms may predict alcohol use outcomes, although depressive symptoms may have a stronger predictive value. While the relationship between these symptoms is complex, optimizing treatment of depression may strongly facilitate treatment for the alcoholism and nicotine dependence.

Source of Funding: National Institutes of Health (R01 AA11929 and in part by R01 AA015385; R01 DA019992; R01 DA019142, R01 AA13370, K02 DA017822, DA CTN); Veteran Affairs Mental Illness Research, Education and Clinical Center.

Literature References:
**Session I–77**

**Efficacy and Tolerability of Risperidone across the Age Span: A Meta-Analytic Comparison of Placebo Controlled Trials**

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**Background:** Many medications are pioneered in adults and then used off label in pediatric patients, with the general assumption of continuity of disease and treatment response. This may not hold true for efficacy or adverse events.

We examined this in the most commonly used second-generation antipsychotic (SGA) in youth, risperidone, by performing a meta-analysis of all double-blind, placebo-controlled studies in adults and youth, comparing efficacy and tolerability across diagnoses and age groups.

**Methods:** Literature search using MEDLINE, Web of Knowledge, and PsycNET for randomized, placebo-controlled trials of risperidone in youth and adults across all diagnoses. Primary outcome were all-cause discontinuation, discontinuation due to inefficacy, discontinuation due to intolerability, and study-defined inefficacy. Secondary outcomes measures included participants with at least one adverse event, and individual adverse events and efficacy measures, including percent weight gain compared to baseline.

**Results:** We identified 32 studies with 1,184 youths (71.7% male, 65.3% White), and 3,909 adults (52.6% male, 85.0% White), spanning six major diagnoses: schizophrenia, bipolar disorder, subaverage intelligence and disruptive behavior disorders, post traumatic stress disorder, autism/pervasive developmental disorder, and Alzheimer’s dementia. There were no age group differences regarding all-cause discontinuation (children: (N=14, n=1,250) RR:0.6 (CI:0.46–0.78), p<0.0001), adults (N=22, n=3,812) RR:0.77 (CI:0.66–0.90), p<0.0011) and discontinuation due to inefficacy (children: (N=10, n=812, RR:0.3 (CI:0.19–0.48), p<0.0001), adults: (N=18, n=2,655, RR:0.52 (CI: 0.41, 0.66, p<0.0001)). Children had significantly greater treatment response, reflected by lower study defined inefficacy (N=12, n=872; RR:0.43 (CI:0.36–0.51), p<0.0001) than adults: (N=20, n=2167; RR:0.64 (CI:0.55–0.75), p<0.0001). This was most pronounced in schizophrenia trials (children: (N=2, n=158; RR:0.34 (CI:0.26–0.45)) adults: (N=11, n=717; RR:0.62 (CI:0.54–0.72)). However, youth were more likely to report at least one adverse event on risperidone than placebo than adults (children: (N=11, n=999; RR:1.3) (CI:1.21–1.39)); adults: (N=10, n=2,433; RR: 1.01 (CI: 0.97–1.06)). Children gained a much greater percentage of baseline body weight (N=5, n=279; 5.67% (CI:3.91–7.43)) than adults (N=2, n=485; 1.45% (CI:0.52–2.84)). Somnolence, however was not different between the age groups (children: (N=13, n=1,132; RR:3.32 (CI:2.25–4.91), adults: (N=14, n=2,165; RR:1.98 (CI:1.46–2.68)).

**Conclusions:** Overall, risperidone showed comparable discontinuation rates in adult and child trials, but even greater study-defined efficacy in pediatric trials. Adverse events were higher in youth, with percentage of weight gained being most notable and concerning, given its long-term health implications.

**Source of Funding:** None.

**Literature References:**


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**Session I–78**

**Effect of Milnacipran on Improving Fatigue in Patients with Fibromyalgia: Results from Three Randomized, Placebo-Controlled Clinical Trials**

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**Background:** Fibromyalgia (FM) is a chronic disorder that includes symptoms beyond widespread musculoskeletal pain. In addition to pain, fatigue is one of the most commonly reported symptoms in patients with FM. Milnacipran, a dual reuptake inhibitor of serotonin and norepinephrine, is approved in the U.S. for the management of FM. This pooled analysis evaluated the effect of milnacipran on fatigue in patients with FM.

**Methods:** Fatigue data were pooled from three phase III studies in FM patients randomized to receive placebo (n=1133), milnacipran 100 mg/day (n=1139), or milnacipran 200 mg/day (n=1837). After a dose escalation phase, patients underwent 12 weeks of stable dose treatment. Fatigue was measured by using the Multidimensional Fatigue Inventory (MFI) total and subscale scores and the Fibromyalgia Impact Questionnaire (FIQ) fatigue items (6 and 7).

**Results:** At the three-month endpoint, significant improvements over placebo with both doses of milnacipran were observed in MFI total score and in FIQ fatigue items six and seven (p<0.01). Milnacipran 200 mg/day treatment resulted in significant improvements in all MFI subscale scores versus placebo (p<0.05); milnacipran 100 mg/day significantly improved general fatigue, physical fatigue, and reduced motivation subscale scores versus placebo (p<0.05). In milnacipran-treated patients, improvements in MFI total score correlated only moderately well with improvements in VAS pain (r=0.451) and Patient Global Impression of Change (PGIC, r=0.507), indicating that these domains provide additional contributions to FM symptomatology.

**Conclusions:** Among patients with FM, milnacipran treatment resulted in significant improvements relative to placebo in multiple dimensions of fatigue. Milnacipran may be effective in treating symptoms of fibromyalgia beyond pain, including fatigue.

**Source of Funding:** Forest Laboratories, Inc. and Cypress Bioscience, Inc.

**Literature References:**


Session I–79

Subject Selection for Central Nervous System (CNS) Clinical Trials

Michael Detke, M.D., Ph.D., Janet B.W. Williams, D.S.W., Kenneth Kobak, Ph.D., Amy Ellis, M.B.A., Earl Giller, M.D., Ph.D., Scott Reines, M.D., Ph.D., Brianne Brown, Ph.D., John Kane, M.D.


Background: Clinical trials fail too frequently (up to 50% failures in trials powered at 80–90%). Baseline severity scores for enrolled patients reveal truncated distributions, as required with a minimum entry criterion. However, same-day assessments by the patients themselves or by remote raters blinded to the entry criterion produced very different distributions.1 This has important implications for drug development. A previous study showed that 34% (range: 5–56%) of patients included by site raters would have been excluded by remote blinded ratings of baseline severity.2 In another study, subjects selected by remote blinded raters (relative to site raters aware of the entry criterion) increased the placebo-drug effect size from 0.43 to 0.74.3 This effect size difference would allow for three-fold reductions in study size with unchanged statistical power.

Methods: Normality of screening and baseline distributions (along with skewness and kurtosis) was assessed in a completed major depression study, for severity measures administered by both remote blinded raters and site raters. Screening and baseline distributions were also assessed for both site and remote raters’ scores in two ongoing depression studies in which site raters administered interviews that were audio taped and later reviewed by remote blinded raters (prior to seeing site raters’ scores). It is important to note that all scores were included in these analyses. The distributions are not truncated by the entry criteria (e.g., “screen-fail” scores were included). Finally, in two studies, diagnostic assessments conducted by remote independent raters were also reviewed.

Results: Adjusted distributions of scores from remote blinded raters at screening and baseline consistently scored higher on normality statistics, and lower on both skewness and kurtosis, than scores from site raters who were unblinded to entry criteria. Structured Clinical Interview for DSM (SCID) assessments by remote raters also revealed potential diagnostic errors in patients previously screened for study entry by site raters.

Conclusions: Subject selection errors are pervasive and substantial. Screening and baseline visit severity scores reveal evidence of bias with unblinding of entry criteria. Diagnosis is an additional source of potential error. Subject selection by remote blinded raters may be beneficial for diagnosis and symptom severity assessment. Accurate subject selection substantially increased effect size in one completed study.

Source of Funding: Industry, MedAvante, Inc.

Literature References:

Session I–80

Placebo Response Assessed by Site and Blinded Remote Centralized Raters in a Generalized Anxiety Disorder (GAD) Trial

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Introduction: High placebo response in anxiety studies contributes to the 50% study failure rate, which is perceived to be growing.1 Remote decentralized raters offer a solution that may address several identified problems. In this study we compared the rate of placebo response assessed by site versus central raters.

Methods: This double-blind, placebo-controlled multi-center study examined the efficacy and safety of two doses of an experimental compound to treat generalized anxiety disorder (GAD). No active comparator was included. Site raters assessed randomized subjects six times over an eight week period. The primary outcome measure was the baseline-to-Week 8 change in site-rated Hamilton Rating Scale for Anxiety (HAM-A). Remote centralized raters also independently rated subjects on the HAMA at baseline and Week 6. One hundred-nineteen site raters were trained and qualified by United Biosource Corporation (UBC) at the investigator meeting. Twenty-two remote centralized raters were trained and calibrated by MedAvante, and maintained high inter-rater reliability throughout the study with quarterly group calibrations and regular observations by trainers.

Results: Site raters admitted 122 subjects to the placebo arm of the study. Of these, remote centralized raters would have admitted 59 (48%) and excluded 63 (52%), based on their HAMA ratings. At baseline, site raters’ mean HAMA score was 24.04 (SD=3.29; N=122), compared to 19.83 (SD=6.037; N=122) for remote raters. In addition, site raters’ mean scores were higher than remote raters’ on all of the individual HAMA items at baseline. At endpoint, remote raters’ scores were similar to site raters’ (14.70 versus 13.95). Exploratory analyses found the mean placebo change by site raters was -9.3. This was significantly higher than the -5.9 point mean placebo change as measured by the remote raters in that same cohort. Site raters classified 47 (39%) subjects as placebo responders (~50% reduction in the HAMA score), as compared to 29 (24%) by remote raters in the site-admitted cohort (nominal p=0.015).

Conclusions: Blinded remote raters showed a 36% reduction in placebo response compared to site raters. At baseline, remote raters have no incentive to score subjects above an inclusion cut-off score, while site raters, may inflate the baseline scores to meet study inclusion criterion. A decrease in placebo response may improve signal detection in clinical trials. In the absence of a positive control, however, it is not clear what the magnitude of change would be in an active treatment arm, so the impact on effect size is unknown.

Source of Funding: MedAvante, Inc. and Sepracor, Inc.

Literature References:

Do Equality Criteria Matter? View from a Third Blind Eye

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Background: Concern over high failure rates in central nervous system (CNS) studies fuels a search for better solutions. Computer administered assessments offer opportunities to collect data consistently across global study sites and may provide a useful standard for exploring hypotheses regarding the performance of studies and clinical trial sites.

Methods: Computer administered Youth Mania Rating Scale (YMRS) assessments (YMRSComp) were added to a double-blind protocol investigating low (MS+ZLo) and higher doses of ziprasidone (MS+ZHi) versus placebo (MS+PBO) as an adjuncts to mood stabilizer (MS = lithium or valproate) treatment for manic and mixed episodes. The primary outcome variable in this protocol was change from baseline to endpoint YMRS score based on the site-based rater’s (SBR) YMRS scores. The analysis plan called for comparison SBR versus computer ratings overall and a comparison of subgroups defined by computer determination of key eligibility criteria (e.g., at screen and baseline subjects meets DSM-IV criteria for a manic or mixed episode, YMRS=18 and YMRS change from screen to baseline <25%).

Results: Of 505 enrolled subjects with ≥1 post-randomization assessment, <37% met the protocol eligibility requirements based on the computer assessments. No statistically significant differences were found between MS+ZLo or MS+ZHi and MS+PBO based on YMRSComp or YMRSComp. A numerically larger change from baseline to day 21 (LOCF) was seen among subjects with a valid diagnosis (MS+ZLo versus MS+PBO = -3.2, MS+ZHi versus MS+PBO = -1.6) compared to those without a valid diagnosis (MS+ZLo versus MS+PBO = -0.3, MS+ZHi versus MS+PBO = -1.7).

Conclusions: The failure to demonstrate efficacy of adjunctive ziprasidone for acute mania is surprising given its proven efficacy as monotherapy. Several issues may contribute to the lack of observed efficacy. The computer assessment data suggests the study was impacted by enrollment of a large number of subjects that, based on computer assessments, did not meet the protocol eligibility requirements. The results show numerically greater separation for MS+ZL subjects meeting each eligibility requirement than those considered ineligible by the computer assessments.

Source of Funding: Concordant Rater Systems; Pfizer, Inc. funded the parent study.

Literature References:


Session I–83
An Investigation of Amino Acid Neurotransmitters as Predictors of Clinical Improvement to Ketamine in Patients with Major Depression
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Background: Dysfunction of amino acid neurotransmitter systems plays a major role in the pathophysiology of major depressive disorder (MDD) and treatment response. Accumulating evidence shows that the NMDA antagonist ketamine produces a rapid and sustained antidepressant response in patients with treatment resistant MDD. In the search for biomarkers of rapid clinical improvement to ketamine, we herein apply proton magnetic resonance spectroscopy (1H-MRS) to investigate whether prefrontal levels of GABA, glutamate (Glu) and the ratio Gln/Glutamate (a surrogate marker of glutaminergic capacity) correlate with the decrease in depressive symptoms after a single intravenous infusion of ketamine in patients with MDD.

Methods: Thirteen participants with a history of treatment-resistant MDD participated in this study. The subjects underwent scanning using a 3-T whole-body scanner with a transmit-receive head coil to three days before receiving a single intravenous infusion of 0.5 mg/kg of ketamine hydrochloride over the course of 40 minutes. All the patients had been drug-free for at least two weeks before the scan session. We measured GABA, Glutamate and Gln/Glutamate ratio in the ventromedial and the dorsolateral/anterior medial prefrontal cortex. Nonparametric Spearman correlation analyses were conducted to determine whether pretreatment GABA, Glutamate and Gln/Glutamate ratio predicted change in depressive symptoms at 230 minutes after ketamine administration.

Results: Depressive symptoms were significantly improved 230 minutes after the infusion, as assessed by change in Montgomery-Asberg Depression Rating Scale (MADRS) score ([t[12]] =3.62, p<0.005) (mean MADRS pre-treatment score 32.6±5.3, mean MADRS score 230 minutes after ketamine 23.3±9.2). Pretreatment GABA or Glutamate were not correlated with antidepressant response in either of the two regions of interest (p>0.1), while pretreatment Gln/Glutamate ratio in the dorsolateral/anterior medial prefrontal cortex was negatively correlated with clinical improvement to ketamine (r(10)=−0.64, p<0.03). Severity of the depressive episode at baseline was positively correlated with the levels of glutamate in the ventromedial prefrontal cortex voxel (r(10)=0.71, p=0.01).

Conclusions: This is the first investigation of amino acid neurotransmitters as predictors of rapid antidepressant response to a drug that specifically targets the glutamatergic system. The findings suggest an association between lower Gln/Glutamate ratio—a surrogate inverse marker of glutaminergic capacity—and greater clinical improvement by ketamine treatment. A lower Gln/Glutamate ratio could be attributable to a lower intracellular pool of glutamine: these data would appear consistent with post mortem evidence that giall cell counts and density are reduced in the dorsolateral/anterior medial prefrontal cortex. We also found that severity of depression was positively correlated with glutamate levels, a finding consistent with evidence that glucose metabolism in this region correlates positively with depression severity in MDD. Limitations of the present study include small sample size and lack of a placebo group.

Source of Funding: National Institute of Mental Health, Intramural Research Program.

Literature References:
Session I–85

The Effects of Nicotine Patch on Cognitive Domains Identified by the Measurement and Treatment Research to Improve Cognition in Schizophrenia Initiative (MATRICS) in Nicotine Abstinent Adults with Chronic Schizophrenia

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Background: The Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative (MATRICS) identified cognitive domains as potential targets for drugs designed to improve cognition and function in schizophrenia. However, the psychopharmacological sensitivity of these different cognitive domains is not well understood. The aim of this study was to challenge the sensitivity of the seven cognitive domains to modulation of nicotinic neurotransmission by studying the acute effects of nicotine withdrawal in schizophrenia.

Methods: Twenty adult patients (mean age 43 years) who were smokers were enrolled in a double blind placebo controlled parallel group study with two conditions; smoking abstinence for 12 hours with or without a nicotine patch. For both conditions, baseline was defined as the assessment conducted at 8–9 p.m. on Day 1 with normal smoking behavior allowed. On Day 2 smoking was then disallowed from waking until 12 p.m. In the nicotine patch condition, subjects were given a 25 mg nicotine patch. In the placebo condition subjects received a placebo patch. Cognitive assessments were conducted at 8 a.m., 9 a.m., 10 a.m. and 12 p.m. Cognitive function in the seven MATRICS domains was measured using the CogState battery.

Results: No differences in cognitive function were observed at baseline. Smoking abstinence was associated with significant deterioration in attention, information processing, planning and problem solving and working memory. With the nicotine patch, all cognitive functions returned to normal limits by 12 p.m.

Conclusions: Nicotinic neurotransmission in schizophrenia modulates executive and attentional functions preferentially in chronic medicated schizophrenia.

Source of Funding: Australian government Export Market Development Grant:CogState Ltd.

Literature References:


Session I–86

Factors Affecting Long-Term Lithium Compliance in Bipolar Illness

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Introduction: The benefit of mood stabilizers in the prophylaxis of bipolar illness is well established. Despite this many patients discontinue their medications, and the consequences can be devastating. The purpose of this study is to examine characteristics predictive of non-adherence.

Methods: Two hundred-forty-four patients with bipolar disorder were included in the present analysis comparing the characteristics of those patients who were lithium compliant (N=133) with those who stopped taking their medication (N=111).

Results: In comparison to lithium compliant patients, patients who stopped taking medication were significantly more likely to be bothered by each of the following: indefinite medication treatment, stigma, having their moods controlled by medication, purely pharmacologic treatment, medication side effects and the idea of having a chronic illness (p<0.01 to <0.001). Patients who stopped taking medication were also significantly more likely to say that they had trouble paying the clinic, that they missed the high, felt less creative and less attractive while on medication, and that they no longer experienced depression and no longer needed medication (p<0.01). Interestingly, patients who stopped taking their medication had significantly more severe depressive symptoms on the last day before stopping their medication in comparison to lithium compliant patients (p=0.01). Lithium compliant patients felt more strongly that bipolar disorder is biological (p<0.001) while patients who stopped taking their medication felt more strongly that it is due to life events (p<0.001). Cross-tabulations examining the association between medication compliance and therapy versus no therapy showed that a large 60% of the patients not receiving any therapy were likely to be lithium compliant while only 42% of the patients receiving some form of therapy were likely to be lithium compliant (p<0.001).

Conclusions: The primary reasons for stopping medication were: indefinite medication treatment (19%), stigma (13%) and aversion to having moods controlled by medication (13%).

Source of Funding: None.

Literature References:

Session I–87

BL-1020, A GABA Enhanced Anti-Psychosis for the Treatment of Schizophrenia: Results of Phase 2b Effective Anti-Psychosis via GABA Level Enhancement (EAGLE) Trial
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Background: BL-1020 is a new chemical entity that combines dopamine antagonism with GABAergic activity. PK studies demonstrate that BL-1020 enters the brain, increases dopamine release in the prefrontal cortex and hippocampus and has the ability to reverse cognitive impairment induced by PCP in animal’s behavioral models. Pre-clinical and clinical studies show that BL-1020 effectively reduces psychotic behavior with significantly fewer side effects.

Methods: The Effective Anti-Psychois via GABA Level Enhancement (EAGLE) study was conducted under a U.S. Food and Drug Administration (FDA), IND application at 40 sites in U.S., Europe and India. In this six-week double blind study, 363 patients were randomized equally to treatment with 10 mg/day or 20–30 mg/day of BL-1020, risperidone (2–8 mg/day) or placebo. The study was designed to demonstrate significant superiority of BL-1020 high dose to placebo on the total score of the Positive and Negative Syndrome Scale (PANSS). Key secondary efficacy measures included the Clinical Global Impressions Scale for Severity (CGI-S) and Cognition (CGI-C), and an exploratory end point: Effect on cognition as measured by the Brief Assessment of Cognition in Schizophrenia (BACS). Risperidone at a dose of 2–8 mg was included as a positive control to validate the study results.

Results: The total PANSS scores, indicated that treatment with BL-1020 high dose (LS mean -23.6; 95% CI -28.4; -18.8) was statistically significant superiority (p=0.002) to placebo; (LS mean -14.4; 95% CI -19.1; -9.7). Risperidone treatment also was associated with significant improvement (LS means -26.2; 95% CI -31.0; -21.3) to placebo. BL-1020 low dose did not separate from placebo. There were no statistically significant differences between BL-1020 high dose and risperidone (p=0.390). These positive results were correlated to CGI-S and CGI-C. BL-1020 high dose showed significant increase in the number of ‘responders’ compared to placebo. The effect of BL-1020 on cognition—BACS composite score, indicated significant superiority of the BL-1020 high dose group compared to placebo (p=0.027) and risperidone (p=0.027) at the end of study, with an effect size of 0.5 compared to placebo. Analysis of safety did not indicate any increased toxicity associated with BL-1020 treatment. The maximum change from baseline in the Extrapyramidal Symptom Rating Scale (ESRS) score was comparable to that of risperidone. BL-1020 increase in prolactin was significantly lower than that of risperidone (p<0.001). There were no statistically significant or clinically relevant changes in the measurements of the electrocardiogram (ECG), laboratory or vital signs (BP, HR, Temp).

Conclusions: These results are consistent with BL-1020 preclinical profile of an effective, safe and well tolerated, antipsychotic with GABA activity and a potential to improve cognition.

Source of Funding: BioLineRx.

Literature References:

Session I–88

Baseline Characteristics of Patients with Schizophrenia Entered into Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC): An Intercontinental Large Simple Trial
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Background: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) was a global, multi-center, randomized, open-label, one-year large simple trial in schizophrenia enrolling over 18,000 patients from 18 countries, in natural practice settings. Using baseline data from the ZODIAC trial, we assessed the severity, prevalence, and treatment of schizophrenia in different clinical settings across the United States, Sweden and Eastern Europe, Latin America and Asia.

Methods: Subjects were randomized to open-label treatment with ziprasidone (n=9120) or olanzapine (n=9119) in naturalistic care. To ensure that the study population was representative of those receiving treatment in “real world” circumstances across the 18 countries, the 749 study sites applied minimal selection criteria and made no attempts to influence or monitor the dosages prescribed. Sweden was excluded from the analyses based on sample size (n=47 patients).

Results: Overall, the mean patient age was 41 years (range 18–96), 55% were male, 5.6% were newly diagnosed, 34% were markedly ill or presented with more severe disease, and 59% were overweight (BMI >25). Across the countries, U.S. (mean age 44, SD 13) patients were older, compared with other cohorts (mean 36–38). The percentage of male patients was similar across countries (51–58%). The percentage of markedly ill or more severe patients were Brazil (45%), the U.S. (32%), Asia (24%) and the other regions (31–35%). History of psychiatric inpatient hospitalization was highest in Eastern Europe (92%), compared with the U.S. (78%) and the other regions (69–72%). History of suicide attempt was greatest in the U.S. (35%), compared with Brazil/South America (26%), Asia (22%) and Eastern Europe (19%). Patients in the U.S. (81%) had the highest prevalence of concomitant medication use, compared with Eastern Europe (52%) and the other countries (72–75%). Among the comorbidities, overweight was 68% in the U.S., compared with Asia (29%) and the other regions (48–53%). High cholesterol/triglycerides levels were found in 21% of U.S. patients compared with a relatively low prevalence in the other countries (2.7–9.6%). Reports of patients who never smoked were: U.S. (31%) and the other countries (50–53%).

Conclusions: Regional variations were found in demographics, the cross sectional treatment of schizophrenia, psychiatric disease history and comorbidities in this global, large simple trial. These findings contribute to the discussion about the complex challenges of conducting and interpreting international clinical trials.

Source of Funding: Pfizer, Inc.

Literature References:
Clozapine and Global Cognition in Schizophrenia

Tarek K. Rajji, M.D., F.R.C.P.C., Hiroyuki Uchida, M.D., Ph.D.,
Zahnoor Ismail, M.D., F.R.C.P.C., Wenzie Ng, B. Pharm.,
David Mamo, M.D., M.S., F.R.C.P.C.,
Bruce G. Pollock, M.D., Ph.D., F.R.C.P.C.,
Benoît H. Mulsant, M.D., M.S., F.R.C.P.C.

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2Keio University School of Medicine, Tokyo, Japan,
3University of London, Toronto, Ontario, Canada

Background: Clozapine (CLZ) has been shown to have a beneficial effect on cognition in schizophrenia in some studies, and a detrimental effect in others. The relative effect and exposure to CLZ and its major metabolite (N-desmethylclozapine [NDMC]) could explain these discrepancies.

Methods: Using a validated measure of global cognition, we performed two binary logistic regression models to assess the relationship among cognition, age, sex, CLZ dose, CLZ and NDMC plasma levels, and their ratio (CLZ/NDMC) in individuals with schizophrenia-spectrum disorders.

Results: Model 1 included age, sex, CLZ dose and CLZ and NDMC levels. Model 2 included age, sex, CLZ dose and CLZ/NDMC. Among 73 subjects (mean age [SD]: 41.6 [12.0]), 16 (21.9%) were cognitively impaired. In Model 1, age and CLZ level were associated with the presence of cognitive impairment (odds ratio [95% confidence interval] for age: 1.079 [1.011–1.152]; CLZ level: 1.003 [1.001–1.005]) while NDMC level was associated with its absence (NDMC level: 0.996 [0.993–0.999]). In Model 2, age, male sex and CLZ/NDMC were associated with cognitive impairment (age: 1.083 [1.015–1.154]; sex: 0.178 [0.032–0.994]; CLZ/NDMC: 7.998 [1.874–34.139]). CLZ dose was not associated with cognition in either model. After controlling for age, sex and dose, CLZ/NDMC was more strongly associated with cognition than CLZ or NDMC levels.

Conclusions: NDMC agonist activity versus CLZ antagonist activity at the muscarinic receptors could explain the strength of the association of CLZ/NDMC with cognition.

Source of Funding: Canadian Institutes of Health Research (CIHR180087) and Centre for Addiction and Mental Health.

Literature References:

A Comparison of Selective Serotonin Reuptake Inhibitor (SSRI) Treatment Effects in Major Depressive Disorder (MDD) Based on Three Different Clinician-Administered Depression Rating Scales

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Regan Fong, Ph.D.,
Ole Graff, M.D.,
Suraja Roychowdhury, Ph.D.,
Susan M. Learned, Pharm.D.,
Rachel P. Moate, M.D., Ph.D.,
John E. Kraus, M.D., Ph.D.,
Robert C. Alexander, M.D., Ph.D.

Background: A number of validated instruments are widely used to measure depressive symptoms in patients with major depressive disorder (MDD). The 17-item Hamilton Rating Scale for Depression (HAM-D-17),1 Montgomery Åsberg Depression Rating Scale (MADRS),2 Quick Interview of Depression Symptoms—Clinician Rated (IDS-CR),3 are commonly used in randomized, controlled treatment trials to demonstrate an effect of study medication over placebo. However, little data exists which directly compares the sensitivity of these scales to detect change and discriminate from placebo in the same study.

Objective: To examine and compare the sensitivity of the HAM-D-17, MADRS and IDS-CR in the same subjects following treatment with an approved selective serotonin reuptake inhibitor (SSRI).

Methods: Results reported include the placebo and active comparator arms of a Phase II study in MDD. This was a 10-week, multicenter, randomized, double-blind, placebo- and active-controlled (paroxetine 20–30 mg/day) flexible-dose study in adults with MDD. The HAM-D-17, MADRS and IDS-CR were administered to all subjects at each scheduled clinic visit (baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10). Sensitivity to treatment effects were examined for the Week 10 endpoint (observed case dataset with a mixed-effect model repeated measure (HLM) (R)) by comparing effect sizes (using Cohen’s d) for change from baseline of the total score and subscales (Bech Melancholia and the Quick Interview of Depression Symptoms—Clinician Rated (QIDS-CR)), the proportion of responders (=50% reduction from baseline), and the proportion of remitters (HAM-D-17 total score =7; MADRS total score =11; IDS-CR total score =14).

Results: Of the 156 subjects randomized to placebo, 115 subjects completed 10 weeks of treatment. For the paroxetine arm, 128/166 subjects completed the study. Effect sizes for total score changes from baseline for the HAM-D-17, MADRS and IDS-CR were similar, ranging from 0.482 to 0.509. Examination of the subscales showed that the Bech Melancholia scale produced the largest effect size at 0.550. The responder and remitter analyses both demonstrated slightly greater treatment effects for the MADRS compared to either the HAM-D-17 or the IDS-CR.

Conclusions: Sensitivity to treatment effects based on rating scale total score change was generally similar between ratings scales, although the HAMD Bech subscale produced the largest effect size. For assessing proportion of responders and remitters with an SSRI, the MADRS may be more useful than the HAMD. The relationship between antidepressant mechanism of action and rating scale total and item scores is discussed.

Source of Funding: GlaxoSmithKline.

Literature References:
A Pooled Analysis of Data from Four Acute Studies in Major Depressive Disorder (MDD) to Assess the Effect of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy on Sleep Disturbance

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Background: Sleep disturbance is a core symptom of major depressive disorder (MDD), which negatively impacts patients’ well-being and functioning. In this analysis, the effect of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy on sleep quality and disturbance in patients with MDD was assessed.

Methods: Pooled data from four acute (six or eight-week) placebo-controlled quetiapine XR (50300 mg/day, administered once daily in the evening) MDD monotherapy studies (D1448C00001, D1448C00002, D1448C00003, D1448C00004) were analyzed. Primary endpoint: change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) scores. Post-hoc analyses based on secondary endpoints included changes in: MADRS item four (4 reduced sleep); Hamilton Rating Scale for Depression (HAM-D) items four (insomnia early), five (insomnia middle) and six (insomnia late); HAMD sleep disturbance factor (items 4+5+6); and Pittsburgh Sleep Quality Index (PSQI) total score. MADRS total score change was analyzed in patients with high (baseline HAMD sleep disturbance factor score ≥4) and low (baseline HAMD sleep disturbance factor score <4) sleep disturbance.

Results: Two thousand-one-hundred-sixteen patients were randomized. Quetiapine XR (all doses combined) significantly improved (LS mean difference versus placebo): MADRS item four (-0.84, p<0.001); HAMD sleep disturbance factor (-0.95, p<0.001) and items four (-0.29, p<0.001), five (-0.35, p<0.001) and six (-0.31, p<0.001); and PSQI total scores (-1.27, p<0.001) from baseline to last assessment. In patients with high levels of sleep disturbance, quetiapine XR (N=865) significantly improved MADRS total score from baseline (LS mean versus placebo) at all timepoints Week 1, 2, 4, 6 (-2.05, -2.50, -2.87, -3.06, respectively; all p<0.001) and 8 (-2.82 Week 8, p<0.01) until the end of treatment (-3.31, p<0.001). In patients with low levels of sleep disturbance, significant improvements in LS mean MADRS total score versus placebo were seen with quetiapine XR (N=252) at Weeks 2 (-3.12, p<0.001), 4 (-2.27, p<0.05) and 6 (-2.07, p<0.05). Safety and tolerability results were consistent with the known tolerability profile of quetiapine.

Conclusions: Quetiapine XR monotherapy significantly improved symptoms of sleep disturbance compared with placebo in patients with MDD. Significant improvement in depressive symptoms was shown in patients with MDD with high and low levels of sleep disturbance.

Source of Funding: AstraZeneca.

Literature References:

Changes in Cognitive and Physical Function during Treatment with Low-Dose Aripiprazole Augmentation in Major Depressive Disorder

Dan Iosifescu, M.D., M.Sc.1, Stella Bitran, Ph.D.2, Christina M. Dording, M.D.3, Michael J. Janca, Ph.D.1, Martina Flynn1, Bijan Bastani, M.D.1, David Walling, M.D.1, John Zajecka, M.D.1, Mark H. Pollack, M.D.1, Maurizio Fava, M.D.1

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Background: Previous reports suggested that fatigue and cognitive dysfunction are prevalent in patients with major depressive disorder (MDD). As a result of their cognitive dysfunction, MDD patients also experience significant psychosocial functional impairment, such as inability to hold a job. We have previously validated the Cognitive and Physical Functioning Questionnaire (CPFQ), a scale measuring subjectively cognitive and physical function in psychiatric patients. We evaluated the effect of low-dose aripiprazole (2 mg/day) versus placebo on fatigue and cognitive dysfunction in patients with inadequate response to antidepressants.

Methods: This research was performed as part of ADAPT-A, a double-blind, placebo-controlled study of low-dose aripiprazole augmentation in patients with inadequate response to antidepressants. Two hundred-twenty-five patients with MDD on antidepressant therapy were randomized in phase 1 to aripiprazole (N=56, 25%) or placebo (N=169, 75%). After six weeks, placebo non-responders were re-randomized to drug (N=61) or placebo (N=63) for an additional six weeks. We used the CPFQ to measure cognitive and physical function at baseline, end of phase 1 and end of phase 2. Severity of depression was measured with the Montgomery-Åsberg Depression Rating Scale (MADRS) at every study visit.

Results: At baseline, patients with treatment resistant depression (TRD) reported marked cognitive and physical dysfunction (30.4±5.3 versus normal=14). As shown in Table 1, cognitive and physical function scores improved numerically in both the low-dose (2 mg/day) aripiprazole and the placebo groups. The improvements in motivation/interest/enthusiasm were significantly higher in the aripiprazole group; all other differences were not significant.

<table>
<thead>
<tr>
<th>Aripiprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Phase 2</td>
</tr>
<tr>
<td>CPFQ total</td>
<td>47.5±3</td>
</tr>
<tr>
<td>Motivation</td>
<td>1.1±1.1</td>
</tr>
<tr>
<td>Alertness</td>
<td>0.4±1.1</td>
</tr>
<tr>
<td>Energy</td>
<td>1.0±1.0</td>
</tr>
<tr>
<td>Attention</td>
<td>0.5±1.1</td>
</tr>
<tr>
<td>Memory</td>
<td>0.3±0.8</td>
</tr>
<tr>
<td>Working Ability</td>
<td>0.6±0.9</td>
</tr>
<tr>
<td>Mental acuity</td>
<td>0.7±0.9</td>
</tr>
</tbody>
</table>

The improvement in cognitive and physical function were moderately correlated (corr. coeff. =0.57) with improvement in depressive scores (MADRS). When analyzed separately both improvements in physical function (corr. coeff. =0.57) and improvements in cognition (corr. coeff. =0.50) were both moderately correlated with improvements in depressive symptoms.

Conclusions: Adjunctive treatment with low-dose aripiprazole in TRD was associated with significant improvement in motivation/interest/enthusiasm; the reduction in other cognitive and physical function scores was not significantly different from placebo. Improve-ments of physical and cognitive function during acute treatment of depression are only moderately correlated with improvement in depressive symptoms.

Source of Funding: Bristol-Myers Squibb.

Literature References:
The Effect of Bipolar Disorder and Vascular Burden on Cognition in Elderly Adults

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Objective: We describe the profile of cognitive function in older adults presenting with bipolar disorder (BD) and mania. We examine whether longer lifetime duration of BD is associated with greater cognitive dysfunction. We also examine whether there are negative, synergistic effects between lifetime duration of BD and vascular disease burden on cognition.

Methods: Eighty-seven non-demented individuals with BD I ages 60 years and older, experiencing manic, hypomanic or mixed episodes, were assessed with the Dementia Rating Scale (DRS) and the Framingham Stroke Risk Profile (FRSP) as a measure of vascular disease burden. Pearson correlations and Generalized Linear Modeling were used to assess the relationship among the variables of interest and to determine predictors of cognitive function, after adjustment for education and severity of mood symptoms.

Results: Subjects had a mean (SD) age of 68.7 (7.1) years and 13.6 (3.1) years of education; 50.6% (n=44) were females; 89.7% (n=78) white and 10.3% (n=9) black. They presented with overall and domain-specific cognitive impairment: in memory, visuospatial ability, and executive function, compared to age-adjusted norms. Lifetime duration of BD was related to the memory sub-scale score, but not to DRS total score, any other sub-scale scores, or vascular disease burden. FRSP scores were related to the DRS memory sub-scale scores, but not total scores or any other domain scores. A negative interactive effect between lifetime duration of BD and FRSP was only observed with the DRS construction sub-scale.

Conclusions: In this study, longer lifetime duration of BD was related to worse memory function in older non-demented adults. Greater vascular disease burden was separately related to worse memory function. Lifetime duration of BD did not have a negative synergistic relationship with vascular disease burden on memory. The association of longer lifetime duration of BD with lower memory performance is consistent with numerous published reports showing a strong association between verbal memory deficits and greater burden of illness in mixed aged adults with BD.1 It is hypothesized that the neurotoxic effect of hypercortisolemia, due to hyper-responsiveness of the hypothalamic-pituitary-adrenal axis observed in BD, may damage neural tissue highly saturated with glucocorticoid receptors, such as the amygdala, hippocampus, and anterior cingulated cortex.4-6

Source of Funding: National Institute of Mental Health (MH068846).

Literature References:

Response Trajectories during Citalopram Treatment for Major Depressive Disorder (MDD): Growth Mixture Modeling in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Cohort

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Background: The evaluation of treatment efficacy may depend critically on the classification of outcomes. Clinical trials typically rely on one (or two consecutive) endpoint measure(s) (i.e., “final score”) to determine remission versus non-remission outcomes. This approach may lead to classification error when subjects exhibit sustained response, or alternating periods of improvement and worsening (i.e., symptom “volatility”).1 Advanced statistical modeling techniques such as growth mixture modeling (GMM), a multilevel modeling technique that incorporates features of cluster analysis, can be applied to longitudinal data to identify latent “classes” or patterns of change in symptom severity over time.2

Methods: Data were analyzed from 4,041 MDD subjects during Level 1 treatment with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. GMM (Mplus version 5.21) was applied to all available scores on the 16-item clinician-rated Quick Inventory of Depressive Symptoms (QIDS-C) obtained at baseline and at Weeks 2, 4, 6, 9, and 12. We used a general latent variable framework to explore and compare models that would handle “not missing at random” (NMAR) data due to dropout.

Results: GMM identified a ‘U-shaped’ trajectory characterized by remission-level improvement achieved at Week 6, and subsequent worsening of symptoms and loss of remission by Week 12. Estimated sizes of a U-shaped trajectory class ranged from 9–19% of subjects depending on assumptions of the model. 62% of subjects belonging to a U-shaped class were classified as having entered remission per the STAR*D protocol.

Conclusions: A portion of subjects who are classified as remitters based upon individual scores (e.g., at Week 6) may belong to a class of subjects that will subsequently worsen by Week 12. Trajectory modeling therefore may provide more complete and accurate assessments of treatment outcome than assessments based upon one to two time points.

Source of Funding: National Institute of Mental Health (1R34MH085933-01: AM Hunter).

Literature References:
Session I–95
Withdrawn
Session II-1

Instability of Serum Lithium Level/Dose Ratio Predicts Affective Episode Recurrence in Bipolar I Disorder

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Background: Identification of individuals at risk for recurrent affective episodes is an important goal for research on maintenance treatment of bipolar disorder. Maintaining consistently therapeutic levels of mood stabilizer medication is a central principle of such treatment. The work presented here aimed to measure the stability of lithium levels in serum and erythrocytes of bipolar patients during maintenance treatment, and to compare these measures between groups of patients with and without affective recurrence.

Methods: Subjects were patients with bipolar I disorder, who participated in a two-year maintenance treatment trial.1 Lithium levels in serum (n=111) and RBCs (n=67) were measured monthly during maintenance treatment. Outcome was categorized according to whether subjects completed two years of successful maintenance treatment with lithium (n=45), experienced a recurrent affective episode (n=46), or dropped out (n=20). The coefficient of variation for the lithium level/dose ratio (CV of L/D) and the erythrocyte lithium variability (ELV) were calculated from sequential monthly blood samples (eight for CV of L/D, five for ELV) that directly preceded the date of recurrence or dropout, or the end of the two-year maintenance treatment interval.

Results: CV of L/D (mean±SD) was higher among patients who experienced recurrence (23.1±14.0) as compared to those who completed two years (16.2±10.9) or dropped out (16.8±7.4) (log transformed data, F=3.80, p=0.026), with post-hoc tests significant for the recurrence versus completer (p=0.047) and a trend for recurrence versus dropout (p=0.080) comparisons. Within the recurrence group, CV of L/D was higher among 29 patients whose episode occurred after 20 or more weeks of maintenance treatment (26.4±16.1) as compared to 17 patients with recurrence before 20 weeks (17.5±6.7) (t=2.57, p=0.014). Mean serum lithium levels were similar in all outcome groups and did not differ by time to recurrence. For the subset of 67 patients in whom ELV was also measured, ELV was correlated with CV of L/D (Spearman ρ=0.443, p<0.001). However, ELV did not differ significantly among the outcome groups (F=0.43, p=0.7).

Conclusions: CV of L/D provides an index of the stability of lithium levels. Instability of such levels predicted affective recurrence, in particular, occurring at or later than the 20th week of maintenance treatment. Because serum lithium levels are almost universally available in clinical treatment settings, this index could provide a useful tool for identifying patients at increased risk for affective recurrence. Appropriate interventions such as efforts to improve medication adherence or identify biological factors affecting lithium disposition could then be initiated. Although ELV was correlated with CV of L/D, it did not have similar utility in identifying patients at risk for recurrence.

Source of Funding: National Institute of Mental Health (MH29618 and MH30915) and the Intramural Program, National Institutes of Health.

Literature References:

Session II-2

Failure to Regulate Positive Emotions: A Functional Neuroimaging Approach to Emotion Dysregulation in Bipolar Disorder

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Bipolar disorder (BD) is a chronic, severe, and often fatal illness. Attempts to accurately diagnose and treat BD are often stymied by its complex and heterogeneous symptoms. One potential solution is to identify pathophysiological processes involved in BD. Such identification may allow for more accurate diagnosis and facilitate the detection of individuals at risk for the development of BD.

The proposed research will utilize functional magnetic resonance imaging (fMRI) to examine neural correlates of positive emotion dysregulation in BD. My theory of emotion dysregulation states that a trait-like marker of BD, present during euthymia, is over-active recruitment of a reward regulation system that results in a pervasive pattern of positive emotional responses and difficulty down-regulating positive emotions. Supportive evidence suggests that: (1) patients with BD exhibit increased psychophysiological and behavioural responses to positive stimuli; (2) people prone to BD report increased excitement at the possibility of earning rewards compared to healthy controls; (3) twin and family studies suggest high heritability estimates for deficits in regulating responses to reward in BD; and (4) abnormalities in self-reported reward-related positive emotions predict increases in symptoms of mania and depression in BD.

This project will use fMRI to extend this theory by demonstrating that: (1) a key feature underlying the pathophysiology of BD during euthymia is greater activation of neural regions involved in tracking and encoding reward (e.g., ventral striatum, nucleus accumbens, orbitofrontal cortex) in conjunction with decreased activation of neural regions involved in regulating emotion (e.g., ventromedial prefrontal cortex) relative to both a remitted major depressive disorder (MDD) and healthy control group; and (2) examine the translational significance of these findings by demonstrating that this pattern of neural activation prospectively predicts increased symptom severity and impaired functioning at a six-month follow-up in BD. In sum, this project spans neuroscience, psychology, and psychiatry disciplines by applying fMRI techniques to better understand the pathophysiology of mood disorders.

Source of Funding: Department Start-Up Funds.

Literature References:
Session II–3

Effects of Different Levels of Alcohol on Psychomotor and Cognitive Performance on the CogScreen Neuropsychological Test Battery
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Cognitive Research Corporation, St. Petersburg, FL

Background: When reporting adverse cognitive and psychomotor effects of a drug, it is helpful to translate the magnitude of the effect into terms that are readily understood by patients and clinicians. Blood alcohol level, as determined by breath analysis, is one such measure. Thus, we attempted to establish the effects of different blood alcohol levels on measures from a widely-used, computerized neuropsychological test battery, the CogScreen battery.

Methods: Normal healthy subjects 21 to 45 years of age were stratified by age and randomized to either alcohol or placebo. Alcohol dosage was titrated to 0.15%. Multiple CogScreen subtests were administered at baseline and when descending alcohol levels reached 0.10%, 0.07% and 0.4%. Subjects on placebo were tested at approximately the same time periods as those in the alcohol group. Both subjects and examiners were blind to treatment assignment. The primary outcome measure was the Pathfinder Number Score (PFN; a computerized analog of the Trail Making Test) assessed by median reaction time for correct responses and coordination error. A secondary outcome measure was the CogScreen Symbol Digit Coding Test (SDC; a computerized analog of the Digit Symbol Substitution Test).

Results: Forty-one subjects were randomized to alcohol and 39 completed treatment, while 39 subjects randomized to placebo completed treatment. Results for the PFN score showed significantly diminished performance in the alcohol group compared to placebo at the 0.10% and 0.07% levels. Results at 0.04% were poorer for alcohol, but not statistically significant. Findings were similar on the SDC. Significant differences between alcohol and placebo were seen at 0.10% and, to a lesser extent the 0.07% level, diminishing to small, statistically insignificant differences at the 0.04% level.

Conclusions: Calibration of neuropsychological tests used to assess adverse cognitive and psychomotor drug effects to different levels of alcohol allows clinicians and patients to better understand the magnitude and significance of those effects in daily life.

Source of Funding: Cognitive Research Corporation.

Literature References:

Session II–4

Bipolar Disorder Educational Needs in Primary Care
Jennifer L. Payne, M.D.,1 Purvi K. Smith, M.S., M.P.H.,2 Rachel DiPaolo2
1Johns Hopkins University School of Medicine, Baltimore, MD; 2Health and Wellness Education Partners, Ramsey, NJ

Background: Bipolar disorder (BD) is a serious, recurrent and often lifelong psychiatric disease characterized by episodic changes in mood and behavior across a wide continuum or “spectrum,” which includes severe depression, severe mania, hypomania, mild to moderate depression, mixed states and rapid cycling patterns. The presence of this spectrum, compounded with distinct challenges for adult and youth populations, makes diagnosis, evaluation and treatment highly complex. Furthermore, BD is often misunderstood and underrecognized in primary care settings with serious implications for patient care.

Objective: To assess educational needs around diagnosis, evaluation and treatment of BD in primary care.

Methods: In January 2009, a survey was mailed to a random sample of 900 family physicians from the circulation of the Journal of Family Practice. Survey recipients were asked about the prevalence of mood symptoms among their patients as well as their extent of preparedness across six clinical competencies related to BD diagnosis, evaluation and treatment. Demographic and learning format preference data were also collected. Descriptive statistics were used to characterize the distribution of results.

Results: Survey respondents reported that an average of 23.0% (n=59, SD=0.15) of their patients complained of mood symptoms. A significant portion of survey respondents indicated that they were underprepared to assess a patient for BD using screening tools (52.2%, 36/69), review with patients comorbidities associated with BD (52.9%, 36/68), evaluate a patient’s phase of BD based on symptoms (50.7%, 35/69), communicate the psychotherapy treatments for BD (64.2%, 43/67), communicate the pharmacologic treatments for BD (57.6%, 38/66) and develop with patients a treatment plan for BD (59.1%, 39/66).

Conclusions: The findings strongly support development of BD educational interventions targeting primary care. Raising physician awareness and competencies pertaining to BD has great potential to improve patient outcomes.

Source of Funding: Eli Lilly (Educational Grant 100127889).

Literature References:
Session II–5

Complementary Use of Tai Chi Improves Resilience, Quality of Life and Cognitive Function in Depressed Older Adults

Helen Lavretsky, M.D., Michael Irwin, M.D.

University of California, Los Angeles

Background: Fewer than 50% of elderly depressed patients achieve remission and functional recovery in response to first-line antidepressant pharmacotherapy. Complementary mind-body interventions can improve partial response to antidepressants via stress-reduction, improved physical functioning, increased socialization, and reduced risks of polypharmacy. This is the first randomized trial of Tai-Chi-Chih used to treat geriatric depression comparing the efficacy of the two alternative treatment strategies designed to achieve symptomatic remission and improvement in resilience and function.

Methods: One hundred twelve older adults with major depression aged 60 years and older were recruited and treated with 10 mg of escitalopram for the first six weeks. Seventy partial responders to escitalopram continued to receive 10 mg of escitalopram a day and were randomly assigned to 10 weeks of either complementary intervention using: (1) Tai Chi Chih for two hours per week; or (2) health education program for two hours per week. All participants received comprehensive evaluations of depression, anxiety, resilience, health-related quality of life and cognition.

Results: Both Tai Chi (TC) and health education (HE) participants demonstrated comparable improvement in the severity of depression (mean Hamilton Rating Scale for Depression [HAM-D] scores of 6.0 in both groups; p=0.99). However, subjects in the TC group demonstrated significantly greater improvement in resilience (mean score of 70.2 versus 65 in the HE group; p<0.05), health-related quality of life (SF-36 scores mean wellbeing scale scores of 80 versus 66; p<0.05) and measures of executive cognitive function (Strop mean errors scores of 0.03 compared to 0.4 errors in the HE group; p<0.05.)

Conclusions: Complementary use of mind-body exercise combined with standard antidepressants may provide additional improvement in clinical outcomes of geriatric depression such as resilience, quality of life and cognitive function.

Source of Funding: National Center for Complementary and Alternative Medicine.

Literature References:


Session II–6

Early Alliance in Prolonged Exposure and Sertraline for Chronic Post Traumatic Stress Disorder (PTSD)

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Therapeutic alliance, or the relationship between client and therapist, is associated with better treatment outcome in both psychotherapy and pharmacotherapy treatment, as well as better medication adherence for many psychiatric disorders. Among those with post traumatic stress disorder (PTSD), the role of the therapeutic alliance may be particularly important due to the difficulty disclosing events surrounding the trauma and the interpersonal nature of many traumatic events. Although alliance has received attention as an important contributor of treatment outcome, no published research to date has examined predictors of alliance in pharmacotherapy treatment for PTSD.

The development of a strong therapeutic alliance may be impacted by an individual’s interpersonal relationships outside of the therapeutic environment. Therefore, in the present study we examined the role of social support from outside relationships (e.g., family and friends) on the formation of a strong therapeutic alliance among 200 men and women with chronic DSM-IV diagnosed PTSD undergoing 10 weeks of either psychotherapy (prolonged exposure) or pharmacotherapy (sertraline). Among those who received prolonged exposure, higher levels of available support, greater satisfaction with current support, higher perceived positive trauma-related social reactions (e.g., emotional support relating to trauma), lower negative trauma reactions (e.g., blame) and higher levels of general support (e.g., talked about interests) were associated with stronger early alliance. Conversely, among those receiving sertraline for chronic PTSD, interpersonal relationships were not significantly associated with the formation of an early alliance.

These results may suggest that different mechanisms are involved in the development of a strong relationship between these two treatment options. For example, outside relationships may more closely mirror the therapist-client relationship in psychotherapy settings. Alternatively, current measures of therapeutic alliance may not be adequately capturing the relationship between client and therapist in pharmacotherapy settings, such that they are omitting potentially important factors unique to pharmacotherapy treatment (e.g., level of expertise). Other clinical implications will be discussed.

Source of Funding: National Institute of Mental Health (R01MH066348).

Literature References:

Effects of Cranial Electrotherapy Stimulation on Resting Brain Activity

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Background: Cranial electrotherapy stimulation (CES) is a Food and Drug Administration-approved treatment for insomnia, depression and anxiety that consists of pulsed, alternating microcurrent applied to the head using electrodes placed on the earlobes. The mechanism of action of CES remains unclear. The objective of this study was to determine the immediate effects of CES stimulation on resting state brain activity.

Methods: We performed functional magnetic resonance imaging (fMRI) simultaneously with CES stimulation in 11 healthy male and female subjects. The experiment consisted of “on” stimulation blocks alternating with “off” blocks for each of 0.5 Hz and 100 Hz pulse frequencies, while subjects rested with their eyes closed. We conducted a voxel-wise and a region-of-interest analysis of the thalamus, as well as a psychophysiological interaction analysis to examine effects on functional connectivity in resting state networks. We also investigated relationships between current intensity and activation patterns using subjects' individualized current as a regressor.

Results: Stimulation of 0.5 Hz was associated with decreased activation in bilateral precuneus, supplementary motor area (SMA), posterior cingulate, pre- and post-central gyrus and the left frontal pole and middle frontal gyrus. 100 Hz stimulation was associated with decreased activation in bilateral SMA and precentral gyrus, right superior parietal lobe, and the right supramarginal gyrus. Current intensity for 0.5 Hz was associated with greater activity in the left SMA, right anterior cingulate cortex, bilateral lateral occipital cortex and the right occipital pole.

Conclusions: CES stimulation is associated with cortical deactivation for 0.5 Hz and 100 Hz frequencies in bilateral frontal, parietal and posterior midline regions. Current intensity may be less critical than frequency of stimulation in relation to cortical deactivation. There appeared to be significant effects on some but not all nodes of the default mode network, suggesting that CES may affect resting state functional coupling. Future studies will need to explore the longer-term effects of daily treatment in relation to clinical improvement, and how brain deactivation relates to previously observed decreases in electroencephalogram (EEG) frequencies, in order to further understand the therapeutic mechanism of action.

Source of Funding: Saban Family Foundation.

Literature References:

Session II–8

Monitoring Social Behavior Using the Child Conflict Index in Children with Attention Deficit Hyperactivity Disorder (ADHD) Treated with OROS Methylphenidate

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Background: This study evaluated social behavior of children treated with OROS methylphenidate (OROSMHP) for attention deficit hyperactivity disorder (ADHD).

Methods: We analyzed combined data from two open-label dose-optimization studies evaluating OROS MPH in children aged nine to 12 years with ADHD (ClinicalTrials.gov records NCT00799409, NCT00799487). OROS MPH (18 mg/d) treatment was initiated with incremental dosage increases of 18 mg/d every three to seven days to an optimal individualized dosage (maximum 54 mg/d). Subjects continued their optimized dosage for up to six weeks. The Child Conflict Index (CCI), which captures conflict/attention-seeking and negativity/withdrawal behaviors, was administered by telephone to parents/caregivers just before baseline, at each dosage-adjustment visit, and at the final study visit. Changes from baseline total CCI scores were evaluated using paired Student t-tests. CCI was a secondary measure and no adjustments were made for multiple testing.

Results: Of 167 subjects in the safety analysis set, 115 were boys and 52 were girls. Mean optimized OROS MPH dosage was 41.1 mg/d (SD=12.9). Mean baseline total CCI score was 8.5 (SD=4.22) for boys and 7.0 (SD=2.92) for girls. Statistically significant (p<0.05) improvements in total CCI score occurred at the first dosage adjustment visit (change of -1.9 [SD=4.24] for boys, -1.0 [SD=2.61] for girls) and at most subsequent dosage-adjustment visits for each gender group and dosage level (18 mg/d, 36 mg/d and 54 mg/d). At the final study visit, both boys and girls had statistically significant improvements from baseline CCI scores (change of -6.2 [SD=3.99] for boys, -4.9 [SD=3.75] for girls; p<0.0001 for both). Two subjects discontinued because of adverse events (AEs) during the dosage adjustment period. AEs reported by <10% of subjects were headache, abdominal pain upper, decreased appetite, irritability and initial insomnia. No serious AEs or deaths were reported.

Conclusions: Statistically significant improvement on the CCI occurred during the first week of OROS MPH treatment and was sustained at the final study visit for both girls and boys. No unexpected or severe AEs were reported.

Source of Funding: Ortho-McNeil Janssen Scientific Affairs, LLC.

Literature References:
Late-Day Attention Deficit Hyperactivity Disorder (ADHD) Symptom Control Improvement with Extended-Release Dexamfetamine in Children with ADHD of All Ethnicities: A Sub-Analysis

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Background: Dexamfetamine (d-MPH) allows similar efficacy to be achieved at half the dose of MPH.1 This study evaluated (post hoc) the efficacy of dexamfetamine extended-release (d-MPH-ER) 30 mg compared with d-MPH-ER 20 mg across children of different ethnicities in a laboratory-classroom setting.2

Methods: In a double-blind, crossover study, children six to 12 years old with attention deficit hyperactivity disorder (ADHD) stabilized on MPH (40–60 mg/d) or d-MPH (20–30 mg/d) were randomized to receive d-MPH-ER 20 mg/d, 30 mg/d, and placebo for seven days each. The final dose of each treatment was administered in a laboratory-classroom setting. Efficacy was measured using the pre- to postdose change of the average Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) combined (attention and deportment) score at 10, 11 and 12 hours postdose (avg 10–12) for all ethnicities.

Results: A total of 165 children were randomized (94 boys; mean age 9.6±1.8 years); 63 Caucasian, 52 African-American, 37 Hispanic and 13 Other (numbers too small to compare). Avg 10–12 changes from predose in SKAMP-Combined scores were numerically greater for d-MPH-ER 30 mg compared with d-MPH-ER 20 mg in all ethnic subgroups: African-American, -5.30 versus -3.07, respectively, p=0.090; Hispanic, -6.57 versus -4.73, respectively, p=0.359; and statistically superior in the Caucasian group, -3.53 versus -0.35, respectively, p=0.005. All Avg 10–12 changes from predose in SKAMP-Combined scores by ethnicity were numerically and statistically superior to placebo in the d-MPH-ER 30-mg and 20-mg analyses.

Conclusions: ADHD symptoms significantly improved with d-MPH-ER 30 mg compared with d-MPH-ER 20 mg at hours 10–12 in all ethnic parameters, with a statistically significant difference in the Caucasian subgroup. Thus, d-MPH-ER 30 mg may provide further benefit to patients of all ethnic backgrounds who do not obtain optimal late-day symptom control with d-MPH-ER 20 mg.

Source of Funding: Novartis Pharmaceuticals Corporation.

Literature References:
Extended-Release Dexmethylphenidate 30 mg Improves Late-Day Attention Deficit Hyperactivity Disorder (ADHD) Symptom Control in Children with ADHD: A Randomized, Double-Blind Crossover Study

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Background: Because no racemization occurs with the pharmacologically active enantiomer of methylphenidate, dex-methylphenidate (d-MPH), similar efficacy can be achieved at half the dose of MPH; a dose of 20 mg d-MPH extended-release (ER) is comparable to 40 mg MPH. The maximum approved MPH dose is 60 mg. Two recent studies suggested a differential response between 20 mg and 30 mg d-MPH-ER during the later part of the day.¹² The current study evaluated the efficacy and safety of 20 mg- and 30 mg- d-MPH-ER in children with attention deficit hyperactivity disorder (ADHD) over a 12-hour laboratory classroom day.

Methods: In a randomized, double-blind, three periods x three treatments, crossover study, six to 12-year-olds with ADHD stabilized on MPH 40–60 mg/d or d-MPH 20–30 mg/d were randomized to receive d-MPH-ER 20 mg/d, 30 mg/d and placebo for seven days each. The final dose of each treatment was administered in a laboratory-classroom. Primary efficacy outcome measured changes in the average Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP)-combined score from predose to 10, 11 and 12 hours postdose (avg 10–12). Adverse events (AEs) and vital signs were noted.

Results: A total of 165 children (94 boys; age 9.6±1.8 years) were randomized, and 162 were included in the intent-to-treat analysis. Mean avg 10–12 change from predose in all efficacy outcome measures were significantly greater for d-MPH-ER 30 mg compared with d-MPH-ER 20 mg: SKAMP-Combined score, -4.47 versus -2.02, respectively, p=0.002; SKAMP-Depertment score, -1.49 versus -0.39, respectively, p=0.019; SKAMP-Attention score, -2.62 versus -1.33, respectively, p=0.001; Math Test-Attempted score, 28.03 versus 18.76, respectively, p=0.002; Math Test-Correct score, 28.02 versus 18.45, respectively, p=0.002. Most common AEs (=3%) were decreased appetite, headache, abdominal pain and tachycardia.

Conclusions: ADHD symptoms improved significantly with d-MPH-ER 30 mg versus d-MPH-ER 20 mg at hours 10–12. d-MPH-ER 30 mg may provide further benefit to patients who do not obtain optimal later-day symptom control with d-MPH-ER 20 mg.

Source of Funding: Novartis Pharmaceuticals Corporation.

Literature References:
Session II–13
The Efficacy of Once-Daily Trazodone in Major Depressive Disorder is Independent of Baseline Sleep Status or Depression Severity

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Background: A controlled-release, once-daily reformulation of trazodone (trazodone ER; OleastroTM) is an effective and well-tolerated therapy for major depressive disorder (MDD). The results of a Likert-type sleep questionnaire demonstrated an improvement in sleep, which was not accompanied by unacceptable daytime somnolence/sedation. To further characterize the antidepressant efficacy of trazodone ER, post hoc analyses were performed to determine whether the efficacy of trazodone ER depends on the intensity of sleep disturbance at baseline or on baseline severity of depression.

Methods: Four hundred-twelve patients with MDD were randomized to receive either trazodone ER or placebo (150–375 mg once daily at bedtime) for a two-week titration and a six-week treatment period. The primary endpoint was change in 17-item Hamilton Rating Scale for Depression (HAM-D-17) from baseline to Week 8. To determine whether the intensity of sleep disturbance at baseline influenced the end-point antidepressant response, an analysis of covariance (ANCOVA) was performed on the change in the HAM-D-6 depression symptoms from baseline to the last study visit (Bech-6), with baseline Montgomery-Asberg Depression Rating Scale (MADRS) reduced sleep item scores as the covariate. As a sensitivity analysis, the ANCOVA was repeated with baseline HAM-D-17 sleep disturbance factor (HDSF) scores as the covariate. The effect of baseline depression severity on efficacy was analyzed using an ANCOVA on the primary endpoint, with baseline MADRS as a covariate.

Results: Baseline mean HAMD-17 scores were 23.2 (active) and 22.4 (placebo); 90% of patients had poor sleep quality. During the treatment period, mean daily dosages were 310 mg (active) and 355 mg (placebo). At Week 8, the active arm demonstrated a greater improvement in HAMD-17 versus placebo (-11.4 versus -9.3; p=0.01), a greater improvement in Bech-6 versus placebo (p<0.05) and a greater improvement in mean HDSF versus placebo (-2.6 versus -1.9, p<0.01). The ANCOVA on the Bech-6 demonstrated that the antidepressant efficacy of trazodone ER is independent of the baseline MADRS reduced sleep item (p=0.61) and the HDSF (p=0.19). Moreover, the primary endpoint did not show a significant dependence on severity of depression (p=0.88).

Conclusions: Trazodone ER is an effective and well-tolerated antidepressant therapy that improves quality of sleep. Furthermore, its efficacy on the core symptoms of depression is independent of a patient’s baseline sleep disturbance status or severity of depression.

Source of Funding: Labopharm Inc.

Literature References:

Session II–14
Fronto-Limbic Connectivity in Adolescents with Depression

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Objective: Major depressive disorder (MDD) frequently begins in adolescence and is associated with severe outcomes including suicide. Substantial brain development occurs during adolescence: by taking advantage of developmental plasticity, early interventions before maturity could be more effective and lasting. Therefore, neurobiological research is urgently needed in the adolescent period to better understand mechanisms that underlie disease and also treatment response.

Background: Prior neuroimaging MDD research has identified abnormalities in a fronto-limbic network of brain regions that mediate emotion processing. Recent advances have allowed for moving beyond just identifying brain structures to investigating the connections within circuits. One approach is to use diffusion tensor imaging (DTI), which measures microstructural integrity of white matter, indexing the anatomical strength of connections between brain areas (“structural connectivity”). Another approach is to use functional magnetic resonance imaging (fMRI) to measure the covariance of activity patterns between distant brain areas (“functional connectivity”).

Preliminary Study: We examined brain connectivity in 14 adolescents with MDD (aged 13–19) compared to 14 matched controls. This pilot study revealed that MDD adolescents had: (1) lower microstructural integrity in the white matter tract between the subgenual anterior cingulate cortex (sgACC) and the amygdala in the right hemisphere; and (2) lower resting-state functional connectivity in the network arising from sgACC. These preliminary data suggest that altered connectivity arising from sgACC is critically implicated in adolescent MDD. Limitations from preliminary work stem from confounds due to medication, exposure to substances and small sample size. Another limitation was the lack of an emotional task, a technique which could allow for examination of how connectivity affects emotional functioning in vivo.

Proposed Methods: To further investigate fronto-limbic connectivity in adolescents with MDD, the next steps are to: (1) reduce confounds by recruiting a medication-free sample; and (2) incorporate an fMRI task that taps into neural connections that mediate emotion processing. For the latter aim, an ideal task is that of viewing faces with fearful expressions, which is known to robustly engage the amygdala. Studies using such tasks have been successfully implemented in adolescent populations to measure functional connectivity between amygdala and prefrontal areas. In a larger (30 depressed and 30 healthy control), unmedicated sample that is free of substance use, we now propose to combine three imaging techniques: (1) DTI, (2) resting-state fMRI, and (3) face-viewing fMRI in a multi-modal neuroimaging study to characterize fronto-limbic connectivity in adolescents with MDD in comparison to healthy controls.

Future Direction: The overarching goal of this research is to understand mechanisms of both disease and treatment response. Results from this project will serve as the foundation for the next phase, which will entail a longitudinal design geared towards examining how treatment interventions in adolescence impact and potentially reverse, abnormalities of neural circuitry.

Source of Funding: NARSAD.

Literature References:

Wednesday, June 16
Session II–15

Psychiatry Resident/Fellow Initiated and Designed Multi-Modal Psychopharmacology Curriculum in Major Depression

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1University of Massachusetts Medical School, Worcester, 2College of Physicians and Surgeons, Columbia University, New York State Psychiatric Institute, 3Wayne State University, Detroit Medical Center, MI, 4New York State Psychiatric Institute, 5The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, NY, 6Indiana University School of Medicine, Indianapolis, 7Tulane School of Medicine, New Orleans, LA, 8University of Kansas Medical Center, Kansas City, 9University of California, San Diego, La Jolla

Background: Portable curricula developed by the American College of Neuropsychopharmacology (ACNP)1 and American Society for Clinical Psychopharmacology (ASCP)2 in partnership with the American Association of Directors of Psychiatric Residency Training (AADPRT) have begun to address some of the inadequacies in the pedagogy of psychopharmacology in residency training.3 The primary aim of the ASCP Committee on Residency and Fellowship was to develop novel, multi-modal psychopharmacology curricula in major depression and bipolar disorder to support psychopharmacology education in U.S. Adult Psychiatry Residency Training Programs. To include adult learner input, Psychiatry Residency/Fellowship Training Program Directors were asked to each nominate one resident or fellow from their program to serve over a period of 12 months. Fifteen resident/fellows were chosen to serve on the Committee.

Methods: The general committee divided into depression and bipolar module workgroups then met monthly by conference call to develop the curricula from September 2009–March 2010. The Depression Module workgroup performed a review of published American Board of Psychiatry and Neurology (ABPN), American Psychiatric Association (APA), AADPRT and Accreditation Council for Graduate Medical Education (ACGME) core competencies and practice guidelines to delineate the scope of the psycho-pharmacology curriculum to be developed. Twelve mini-modules were chosen to make up the Depression Teaching Module, each of which could be used as free-standing, teaching sessions or collectively as one comprehensive curriculum. The core of each mini-module was a PowerPoint Presentation which addressed the clinical characteristics, diagnosis or psychopharmacologic treatment of depression; corresponding multi-modal learning activities stemmed from each mini-module. In addition to core neuropsychopharmacological and clinical psychopharmacological teachings, mini-modules on research findings from recent clinical trials and evidenced-based medicine in psychiatry were incorporated to strengthen critical scientific literature review skills. Problem and group-based learning and alternative teaching exercises were developed for each mini-module to re-enforce didactic learning objectives and extend learning beyond the scope of the slide set. These modalities included: multiple choice question banks, Jeopardy®-style psychopharmacology quizzes, clinical vignettes with interactive learning exercises and “sham” clinical scenarios designed to assess the ACGME core competencies.

Conclusions: A psychiatry resident/fellow designed Depression Module was developed to flexibly suit the needs of individual Residency Programs and improve psychopharmacology teaching in residency programs by placing an emphasis on multi-modal learning activities. The Module is scheduled to undergo field testing at Psychiatry Residency Programs later in the year to test feasibility and effectiveness.

Source of Funding: None.

Literature References:

Session II–16

Effect of Food on Lurasidone Absorption

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Objective: Lurasidone is a novel antipsychotic under development for the treatment of schizophrenia. The aim of this study was to determine the effect of calorie and fat content on the steady-state pharmacokinetics of lurasidone in subjects with schizophrenia.

Methods: This was an open-label, multiple dose inpatient study in which subjects (N=21) were randomized to take lurasidone 120 mg under six meal conditions (fasted, low calorie/high fat, medium calorie/low fat, medium calorie/high fat, high calorie/low fat, and high calorie/high fat) in randomized sequences over six crossover periods. The low calorie meal contained 350 calories; the medium calorie meal contained 500 calories and the high calorie meal contained 1000 calories. The low fat meal contained 15% fat content, the high fat meal contained 50% fat content. Serial blood samples of lurasidone and its metabolites were collected for 24 hours post-dose.

Results: The presence of food resulted in an increased mean Cmax (ng/mL) and AUC0-tau (ng·hr/mL), compared to the fasted state (62; 468) for the low calorie/high fat meal (173; 850), the medium calorie/low fat meal (166; 740), the medium calorie/high fat meal (148; 813), the high calorie/low fat meal (140; 773), and the high calorie/high fat meal (150; 878). Relative to the fasted state, Cmax increased by 2.2 to 2.8-fold and AUC0-tau increased by 1.6 to 1.9-fold in the presence of food.

Conclusions: Although food increases the absorption of lurasidone by approximately two-fold, the specific calorie and fat content of the meal appeared to have only modest effect on lurasidone exposure parameters.

Source of Funding: Dainippon Sumitomo Pharma.

Literature References:
Session II-17

GLYX-13, an NMDA Receptor Glycine Site Functional Partial Agonist, Does Not Elicit Psychotomimetic Side Effects in Normal Human Volunteers at Doses Expected to be Therapeutic in Treatment-Resistant Major Depressive Disorder

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Background. The NMDA modulators ketamine1 and CP-101,6062 produce rapid reduction in depression, within hours to days, with long duration of effect, up to one week or more. GLYX-133 is efficacious in the rat Porsolt model and other models with ED50 1 mg/kg IV, with onset within one hour following a single dose and duration of action of several days. Unlike ketamine and CP-101,606, GLYX-13 does not elicit signs of dopamine system activation (enhanced locomotor activity or reduced prepulse inhibition) in rats.

Methods. The safety and pharmacokinetics of GLYX-13 were assessed in normal human volunteers following single IV doses in four dose cohorts of five subjects, including one who received placebo and four who received GLYX-13 at 0.5, 1, 5, or 10 mg/kg depending upon cohort. Psychotomimetic side effects were specifically evaluated.

Results. Six female and 14 male subjects, aged 19–57 years were enrolled. Adverse events (AEs) were similar for placebo and GLYX-13 and all were rated mild. No psychotomimetic side effects were noted. Cmax and AUC were directly related to dose. At 10 mg/kg, Cmax was 100 versus 55 μg/ml, AUC was 1114 versus 278 μg/ml/hour, t1/2 was 22 versus 16 min in humans versus rats.

Conclusions. GLYX-13 was well tolerated and caused no psychotomimetic effects following single doses 10 times the EC50 for antidepressant-like effects in rats. GLYX-13 may be useful as a therapeutic agent for treatment resistant depression with rapid onset and prolonged duration of action, without causing psychotomimetic side effects at therapeutic doses.

Source of Funding: Naurex, Inc.

Literature References:

Session II-18

In-Depth Analysis of Short-Term Tolerability of Desvenlafaxine 50 mg/d in Patients with Major Depressive Disorder

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Pfizer, Inc., Collegeville, PA

Background: Desvenlafaxine (administered as desvenlafaxine succinate) is approved for the treatment of major depressive disorder (MDD) in adults at the recommended dose of 50 mg/d. The objective of this analysis is to assess the tolerability of desvenlafaxine 50 mg/d compared with placebo in MDD patients, including number needed to treat for harm (NNH) and global benefit-risk data from all phase three placebo-controlled clinical trials that used the 50 mg/day fixed dose.

Methods: Data were pooled from three double-blind, placebo-controlled, eight-week trials in which outpatients with DSM-IV MDD were randomly assigned to fixed-dose desvenlafaxine (50 mg/d) or placebo. Incidence rates for the most common adverse events (AEs) reported by desvenlafaxine-treated patients at =2 times the rate of placebo were tabulated by week and by severity. Global benefit-risk ratio scores were calculated based on three benefit outcomes (17-item Hamilton Rating Scale for Depression [HAMD-17] response and remission status and Clinical Global Impressions-Improvement response status) and severity of AEs. Number needed to treat for benefit (NNT) was calculated based on the three benefit outcomes, and NNH was calculated based on discontinuations due to any AE or due to the most common AEs.

Results: The safety population included 939 patients (desvenlafaxine: n=465; placebo: n=474). Percentage of patients discontinuing due to any AE was 3.0% for desvenlafaxine and 1.3% for placebo. Nausea (21.9%), dizziness (11.4%), insomnia (9.2%), hyperhidrosis (8.0%) and constipation (7.7%) were the most common AEs reported by desvenlafaxine-treated patients (placebo: 9.9%, 5.3%, 3.4%, 3.8% and 3.4% respectively). Incidence of the most common AEs declined to placebo levels by Week 2. For desvenlafaxine, rates of nausea were 16.3% during Week 1 (placebo, 4.0%) and 2.4% during Week 2 (placebo, 3.2%). Only three patients on desvenlafaxine reported common AEs that were severe. Global benefit-risk ratio scores were calculated for 933 patients (desvenlafaxine: n=462; placebo: n=471) with evaluable efficacy data. Global benefit-risk ratio scores were greater for desvenlafaxine across all range, 0.67 to 2.02 compared with placebo (range, 0.58 to 1.99) for each benefit outcome. NNH ranged from nine to 16 for the three benefit outcomes. NNH based on discontinuation due to any AE was 57; NNH based on discontinuation due to the most common AEs was 66.

Conclusions: Desvenlafaxine at the recommended 50-mg dose was well-tolerated. Rates of the most common AEs for desvenlafaxine were comparable to placebo after Week 1.

Source of Funding: Pfizer, Inc.

Literature References:
Session II–19

An Assessment of the Pharmacokinetics and Tolerability of Single Ascending Doses of Desvenlafaxine Administered to Healthy Chinese Subjects

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Background/Objective: In a previously conducted single ascending dose study based in the U.S., desvenlafaxine, which is administered as desvenlafaxine succinate, was shown to have a linear pharma-ko-kinetic profile. The dose proportionality of exposure to desvenlafaxine has also been demonstrated in a population of healthy Japanese females. The objective of the current study was to assess the pharmacokinetic behavior and tolerability of single ascending doses of desvenlafaxine in Chinese subjects.

Methods: This placebo-controlled, inpatient single ascending dose study was performed in a population of healthy Chinese subjects that were randomly assigned to receive either a single dose of desvenlafaxine 50, 100, 200 mg or placebo. Desvenlafaxine concentrations in urine and plasma were measured using a validated liquid chromatography/tandem mass spectrometry method. Peak plasma concentration (Cmax) and time to Cmax were determined directly from observed data, and area under the plasma concentration-versus-time curve (AUC) and other pharmacokinetic parameters were computed. A preliminary assessment of dose proportionality for Cmax and AUC was conducted using a power model and a lack-of-fit test was used to determine the validity of the power model. Tolerability was assessed through the reporting of adverse events (AEs).

Results: Thirty-six male and female subjects, 19–30 years of age, were enrolled. The Cmax of desvenlafaxine increased 242% between those receiving 50 (114 ng/mL) and 100 mg (276 ng/mL). The Cmax for subjects receiving desvenlafaxine 200 mg was 703 ng/mL, which represented a 255% increase compared with those receiving 100 mg. The AUC of desvenlafaxine increased 221% from the 50 mg dose (2,660 ng·hr/mL) to the 100 mg dose (5,890 ng·hr/mL), and increased 228% from the 100 mg dose to the 200 mg dose (13,400 ng·hr/mL). The power model analysis indicated dose proportionality for AUC, but not for Cmax; lack-of-fit tests were not significant for either AUC or Cmax. A total of 64% of subjects reported at least one AE, which primarily included dizziness (42%), nausea (28%) and somnolence (17%). Those receiving desvenlafaxine 100 and 200 mg were generally more likely to experience AEs than those receiving 50 mg.

Conclusions: Desvenlafaxine demonstrated dose-proportional exposure (AUC) and was generally well tolerated in this population of healthy Chinese subjects.

Source of Funding: Pfizer, Inc.

Literature References:

Session II–20

Assessing Motivation in Schizophrenia

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Background: Impaired motivation is a core negative symptom in schizophrenia,1 and primarily manifests as a deficit in spontaneous, goal-directed behavior in daily-life activities. However, its measurement is still debated.2 Most rating scales include patients’ self-declared interests, their self-reported level of engagement and clinicians’ observations, but the validity of patients’ reports has been questioned. Consequently, investigators have suggested that computerized tasks or smell identification may be better measures of motivation.

Methods: Forty-four individuals with schizophrenia hospitalized in a research unit and 20 healthy controls completed an affective computerized task3 to measure implicit motivation and the Behavioral Activation Scale (BAS) to measure approach motivation. Inpatients with schizophrenia completed questionnaires measuring their interests in ward activities and their engagement in those activities. Clinicians rated patients’ active engagement in those same activities. Measures of spontaneous, goal-directed, interpersonal and impersonal behavior obtained using time sampling methodology provided the reference measure of motivation. Patients also completed the Brief Smell Identification Test, and neurocognitive tasks measuring executive functions, processing and motor speeds.

Results: Compared to controls, patients with schizophrenia did not show impaired implicit motivation and had higher scores on the BAS. Level of spontaneous behavior significantly correlated with ward behavior rated by clinicians (r=0.76, p<0.001) but not with patients’ self-rated interests (r=0.03, p=0.83) and self-rated level of engagement (r=0.20, p=0.20). Smell identification significantly correlated with social behavior rated by clinicians. Observed motivation measures significantly correlated with negative symptoms but not with cognitive tasks. Self-reports of interests significantly and inversely correlated with Positive and Negative Syndrome Scale (PANSS) total scores but not with negative symptoms.

Conclusions: Motivation in schizophrenia is best measured by direct observation of patients’ self-initiated behavior and is independent of neurocognitive functions. Self-reports, motivation questionnaires and level of engagement in experimental tasks do not capture motivational impairment in schizophrenia.

Source of Funding: None.

Literature References:
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)

Maurizio Fava, M.D.1, David Mischoulon, M.D., Ph.D.1, Dan Iosifescu, M.D.1, Janet Witte, M.D.1, Michael Pencina, Ph.D.2, Gary Asnis, M.D.3, Michael Levy, M.D.1, Karl Rickels, M.D.1, Mark Pollack1

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Background: This multicenter, placebo-controlled study was aimed at assessing the efficacy of low-dose aripiprazole (2 mg/day) adjunctive to antidepressant therapy (ADT) in the treatment of refractory depressive disorder (MDD) patients with a history of inadequate response to prior ADT.

Methods: In accordance with the sequential parallel comparison design (SPCD), 225 subjects with MDD (mean age: 45 ± 11; 64% women; 19% non-white; 56% employed; 29% without college education), with inadequate response to ADT, were recruited across 21 sites and randomized to 60 days of double-blind treatment with either aripiprazole (Abilify) 2 mg/d or placebo, divided into two phases of 30 days each. There was a 2:3:3 rate of random assignment to the treatment regimens (drug/placebo in phase 1 and 5 mg/d in phase 2), placebo/placebo (placebo in both phases), and placebo/placebo in phase 1 and aripiprazole 2 mg/d in phase 2. Safety and efficacy assessments, including the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions Scale for Severity (CGI-S) and Improvement (CGI-I), Symptom Questionnaire (SQ), Cognitive and Physical Functioning Questionnaire (CPFQ) and Patient Health Questionnaire (PHQ-9), were performed every 10 days throughout the 60 days of treatment. During the first phase of double-blind treatment, eligible subjects (outpatients with MDD) diagnosed with the use of the Structured Clinical Interview for DSM Disorders, Patient Edition (SCID; I/P) and deemed “valid” using the SAFER criteria interview administered by independent raters. Severity thresholds were operationalized as a Hamilton Rating Scale for Depression (17-item HAM-D-17) score ≥ 23. Quick Inventory of Depressive Symptomology—Self Report (QIDS-SR—17) ≤ 15. Subjects who were receiving ADT for at least eight weeks, with a stable, adequate dose over the last four, and a treatment history for the current episode of an inadequate response to at least one and no more than three adequate antidepressant treatments, as defined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) administered by remote, independent raters.

Results: For Phase I, the Aripiprazole/Aripiprazole arm had a response rate of 18.5%, the Placebo/Placebo arm response rate was 17.4%, the Placebo/Aripiprazole arm response rate was 17.4%. In Phase II, the Placebo/Aripiprazole arm response rate was 18%, and the Placebo/Placebo arm response rate was 7.9%. The pooled, weighted difference between aripiprazole 2 mg/d and placebo in percent of responders (defined as a ≥ 50% decrease in the MADRS) in the two phases was 5.6% (p = 0.18; NS). With respect to the secondary analyses, the MADRS mean changes (IoC) for aripiprazole 2 mg/day were −8.5 in phase 1 and −5.8 in phase 2, whereas the MADRS mean changes for placebo were −8.3 in phase 1 and −3.3 in phase 2 (weighted difference, attributing equal weight: −1.5; p = 0.08; NS). Other secondary endpoints showed non-significant pooled differences between aripiprazole 2 mg/d and placebo in terms of differences in remission rates (MADRS < 11), differences in changes from baseline in CGI-S and CGI-I, as well as changes from baseline in total scores at endpoint of MGH QIDS-SR—17. The SQ well-being mean improvements for aripiprazole 2 mg/day were 3.7 in phase 1 and 3.3 in phase 2, whereas the SQ well-being mean improvements for placebo were 2.8 in phase 1 and 2.0 in phase 2 (weighted difference, attributing equal weight: −1.2; p = 0.0548; NS). From a safety perspective, of the 225 randomized subjects in phase I, two dropped out in the aripiprazole 2 mg/day arm and one in the placebo arm. Furthermore, of the 138 phase I placebo non-responders, 14 dropped out in phase II: Nine in the aripiprazole 2 mg/day arm and 5 in the placebo arm. There were only minimal differences in rates of adverse events (AEs) between aripiprazole and placebo, with the exception of constipation and dry mouth, which were more common on aripiprazole. No significant differences in rates of AEs such as restlessness, akathisia, insomnia and fatigue were noted.

Conclusions: In conclusion, this study provides clear support for the tolerability of low-dose aripiprazole (2 mg/day) as augmenting agent for patients with inadequate response to ADT. However, in terms of efficacy, it appears that the efficacy of this strategy may be marginal.

Source of Funding: Bristol Myers Squibb.

Efficacy of Extended Release Quetiapine Fumarate (Quetiapine XR) in Patients with Major Depressive Disorder (MDD): Results from Eight Double-Blind Randomized Studies

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Background: Major depressive disorder (MDD) is a complex and debilitating neuropsychological condition. Approximately 60% of pharmacological treatment options for MDD fail to demonstrate improved efficacy versus placebo.1 Once-daily extended release quetiapine fumarate (quetiapine XR) was evaluated as monotherapy (50, 150 and 300mg/day) (acute and maintenance treatment) or as adjunct to antidepressant (AD) therapy (150 and 300mg/day) in patients with MDD.

Methods: Data from eight (seven acute, one maintenance) double-blind, placebo-controlled studies of quetiapine XR were analyzed. Primary endpoints: change from randomization in Montgomery-Åsberg Depression Rating Scale (MADRS) score (acute studies); time from randomization to depressed event (maintenance study). Statistical analyses included ANCOVA for difference between quetiapine XR and placebo in LS mean change in MADRS total score from randomization to study end (last observation carried forward [LOCF]; acute); hazard ratio (HR) for time to recurrence of a depressed event (maintenance).

Results: Figure 1 demonstrates the treatment differences (95% CIs) for the primary efficacy endpoint for the seven acute studies. Four monotherapy studies were significant in favor of quetiapine XR, MADRS LS mean versus placebo: Study 1 (quetiapine XR 50, 150 and 300 mg/day, −2.50, p<0.005; −3.44, p<0.001 and −3.11, p<0.01); Study 2 (quetiapine XR 150 and 300 mg/day, −3.63, −4.11; both p<0.001; duloxetine 60 mg/day, −3.46; p<0.001); Study 3 (quetiapine XR 150/300 mg/day, −3.39, p<0.01); and Study 14 (quetiapine XR 50–300 mg/day, −7.54, p<0.001). Study 4 (monotherapy) was a failed study in which both quetiapine XR and the active comparator (eslicarbazepine 10/20 mg/day) failed to separate from placebo (quetiapine XR 150/300 mg/day, −1.61, p=0.174; eslicarbazepine, −1.13, p=0.346). Studies of quetiapine XR as adjunct to AD were also significant in favor of quetiapine XR: Study 6 (quetiapine XR 150 mg/day, −1.90, p=0.006; 300 mg/day, −2.96, p=0.002). Study 7 (quetiapine XR 150 and 300 mg/day, −3.03, −2.75, both p<0.01). Quetiapine XR maintenance therapy (Study 5) also significantly increased the time from randomization to a depressed event; HR (95% CI): 0.34 (0.25, 0.46); p<0.001. Safety and tolerability findings in all studies were consistent with the known profile of quetiapine.

Conclusions: Quetiapine XR (monotherapy or adjunct) was consistent in significantly improving depressive symptoms compared with placebo in six out of seven acute MDD studies. Quetiapine XR maintenance therapy significantly reduced the risk of a depressed event.

Source of Funding: AstraZeneca.

Literature References:


Source of Funding: AstraZeneca.

Literature References:


Session II–23

Effects of Dextro-Amphetamine on Cortical Oscillations in Schizophrenia versus Healthy Control Subjects


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It has been hypothesized that cortical function may have an inverted-U shaped dependence on dopamine (DA) levels. There is evidence that schizophrenia (SZ) is associated with decreased cortical DA levels, while healthy control subjects (HC) may already have optimal DA levels. Thus, administration of pharmacologic agents that increase cortical DA may improve cortical function in SZ subjects while impairing cortical function in HC. To test this putative relationship, we examined the effect of single-dose dextro-amphetamine (d-Amph) on cortical responses in an auditory click-train paradigm. We report preliminary results from eight HC and six SZ subjects who participated in a double-blind, cross-over, placebo (PBO)-controlled study of single-dose d-Amph administration. After medication administration, subjects had EEG measured during auditory click trains presented at 20, 30, and 40 Hz. The spectral power of the steady-state auditory evoked potential was determined with wavelet analyses. For the PBO condition, SZ showed lower gamma (40 Hz) power compared to HC, replicating previous studies. However, SZ showed improvements in gamma power with d-Amph administration compared to placebo, while HC showed less gamma power with d-Amph compared to PBO. Our results provide preliminary evidence that increasing cortical dopamine may enhance cortical activity in schizophrenia subjects while impairing cortical responses in healthy subjects, consistent with an inverted-U shaped relationship between cortical activation and dopamine levels. Results will be discussed in terms of possible neurophysiologic effects of dopamine and therapeutic relevance for schizophrenia.

Source of Funding: National Institute of Mental Health (K08 MH080329).

Literature References:


Session II–24

Quetiapine XR as Adjunct to Antidepressants in Patients with Major Depressive Disorder (MDD) and Inadequate Response to Therapy: Pooled Analysis of Data for Patients with Low and High Levels of Baseline Anxiety

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Background: Patients with major depressive disorder (MDD) and high levels of anxiety typically experience more chronic disease progression, greater severity of symptoms and more functional impairment compared with patients with low anxiety levels.

Methods: Pooled data from two similar six-week, double-blind, randomized placebo-controlled trials (Study D1448C00006 and Study D1448C00007) in patients with MDD and an inadequate response to ADs were analyzed. Patients received quetiapine XR (150 or 300 mg/day) + AD or placebo + AD. Secondary analyses included change at Week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total (primary), Hamilton Rating Scale for Anxiety (HAMA) total and Clinical Global Impressions Scale for Severity (CGI-S) total scores in patients with high (HAMA total score ≥20) and low (HAMA total score <20) baseline anxiety levels.

Results: For patients with high baseline anxiety levels (HAMA total score ≥20; n=433), adjunct quetiapine XR 300 mg/day (-15.92, p<0.05) but not 150 mg/day (-15.20, p=0.122) significantly reduced MADRS total scores versus placebo + AD (-13.49) at Week 6. Adjunct quetiapine XR 300 mg/day significantly improved HAMA total (-12.19 versus -10.18, p<0.05) and CGI-S total scores (-1.68 versus -1.37, p<0.05) versus placebo + AD at Week 6. The reductions in HAMA total and CGI-S total scores with adjunct quetiapine XR 150 mg/day were -11.70 (p=0.082) and -1.60 (p=0.131) at Week 6, respectively.

For patients with low baseline anxiety levels (HAMA total score <20; n=486), adjunct quetiapine XR 150 mg/day (-13.99, p<0.001) and 300 mg/day (-13.98, p<0.001) significantly improved MADRS total scores versus placebo + AD (-10.83) at Week 6. Adjunct quetiapine XR 150 mg/day significantly improved HAMA total (-6.59, p<0.01) and CGI-S scores (-1.63, p<0.001) versus placebo + AD (-4.93, -1.16, respectively) at Week 6; significant improvements were also seen with adjunct quetiapine XR 300 mg/day in HAMA total (-6.48, p<0.05) and CGI-S scores (-1.52, p<0.01). Reported adverse events (AEs) were similar in both baseline anxiety level groups and were consistent with the known tolerability profile of quetiapine XR.

Conclusions: In patients with MDD and an inadequate response to AD therapy, adjunct quetiapine XR effectively reduced depressive and anxiety symptoms in patients with high (quetiapine XR 300 mg/day) and low (quetiapine XR 150 and 300 mg/day) levels of baseline anxiety.

Source of Funding: AstraZeneca.

Literature References:
Impact of Information Demands on Site versus Expert Inter-Rater Reliability of the Positive and Negative Syndrome Scale (PANSS)

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Background: Training and alignment of raters is critical in ensuring adequate inter-rater reliability (IRR) and eventual study success in schizophrenia clinical trials. Training at investigator meetings often ignores interview skills and does not prevent rater drift during the study. Videotaping/videoconferencing address these issues by providing expert independent ratings with immediate site rater (SR) feedback. However, accurate Positive and Negative Syndrome Scale (PANS) scoring requires not only good observation and interview skills but also informant reports which may be lacking for remote expert raters.

Methods: Twenty-eight separate ratings of the structured clinical interview for the PANSS were conducted by nine SRs in Russia and Ukraine. Each PANSS interview was conducted in a local language, videotaped and rated separately by an in-country expert rater (ER) who was blinded to SR scores and provided feedback directly to SRs.

Results: The intraclass correlation coefficient (ICC) for overall PANSS score showed moderate agreement between SR and ERs (ICC=.438, p<0.05) according to conventions. The majority of SR versus ER ICCs for individual PANSS items (60%) also fell in the moderate range (ICC 0.40–0.59); while 20% fell in the good to excellent (ICC 0.60–1) range, and 20% fell in the poor range (ICC <0.20). No readily apparent patterns of ICCs were noted based on positive/negative/general psychopathology composites, or rater demographics such as PANSS experience and rating performance at the investigator meeting. PANSS items were then divided into three categories according to the type of information needed to score appropriately. One category contains two items (N4 and G16) that are based solely on informant report (I), the second category has 16 items (P2, N1, N3, N5–7, G1–4, G9–13 and G15) and utilizes information gathered during the clinical interview (C); the third category is composed of the 12 remaining items and utilizes information from both informant and clinical interview (IC). Average ICCs suggested relatively poorer reliability between SR and ERs for items based on informant report only (ICC =0.04); fair reliability (ICC ICC=0.376) for combined items, and moderate reliability (ICC C=0.403) for items gathered based solely upon clinical interview. Despite these qualitative differences no statistically significant differences were seen between these three ICCs (x2=1.68, p=0.43).

Conclusions: This data underscores the need for access to all available sources of information for remote ERs in order to ensure valid and reliable PANSS assessments and feedback to SRs.

Source of Funding: None.

Literature References:

Inter-Rater Reliability in the Assessment of Pediatric Schizophrenia Using the Positive and Negative Syndrome Scale (PANSS): Training Results from a Russian Cohort

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Background: The onset of schizophrenia is often in late adolescence or early adulthood though in some cases can be earlier with pediatric schizophrenia affecting approximately two in one million in the general population. The assessment of schizophrenia in childhood or early adolescence demands a somewhat different style of interviewing technique but the core psychopathology is essentially similar to what may be seen in older patients: delusions, hallucinations and a range of other symptoms including social withdrawal and cognitive problems. The Positive and Negative Syndrome Scale (PANSS) is a primary measure in research used to assess these symptoms. In this study we looked at training data to determine if raters in this group were more or less likely to achieve similar reliability to that expected in adult samples. Because this was a Russian cohort and the materials were originally produced in English, we were also interested in potential linguistic or cultural effects as this has emerged as an important issue in the global standardization of research practices.

Methods: Two early adolescent-aged patients with DSM-IV diagnoses of schizophrenia were rated by video using the PANSS in a training exercise with 30 Russian psychiatrists. All materials were translated into Russian and validated and scores were obtained by rating videos that were subtitled in Russian with transcripts available. Inter-rater reliability was obtained by using the intra-class correlation coefficient (ICC) statistic for total scale and for the positive, negative and general subscales.

Results: Raters achieved comparable inter-reliability to that reported in the literature for the rating of videos. There appeared to be little difference in ICCs for total scale and positive, negative and general subscales. The negative subscale was slightly less reliable in this group with 0.976 and 0.979 for pre- and post-training respectively, but this is still in the excellent range. Pre- and post-training ICCs for the positive subscale ICCs were 0.987 and 0.989, general 0.986 and 0.970 and total scale 0.987 and 0.976.

Conclusions: A number of previous studies utilizing this methodology (rating from video) have reported ICCs in this range for the PANSS rating adults. Our data suggests that there does not appear to be a significant impact of rating child versus adult patients using the PANSS instrument with very high ICCs obtained in this small cohort of Russian psychiatrists. Linguistic and cultural considerations did not appear to impact overall reliability but may have had a limited effect on individual item reliability. Caution must be exercised in the interpretation of these results due to the limited sample size and because ICCs can be inflated by the reduction of information variance inherent in rating from video.

Source of Funding: ProPhase LLC.

Literature References:
Placebo Response in Antipsychotic Trials

Cynthia Siu, Ph.D.1, Ofer Agid, M.D.2, Gary Remington, M.D.2, Shirlie Kapur, M.B.B.S., Ph.D.3, F.R.C.P.C.1, Eric Wattsy, M.D.1, Douglas Vanderburg, M.D., M.P.H.1, Steven G. Potkin, M.D.1

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**Background:** Large placebo responses in antipsychotic trials present a major challenge for psychopharmacologic drug development. The analysis aimed to identify moderators of placebo response in antipsychotic trials and to investigate the trajectory patterns of long-term placebo response.

**Methods:** We searched the MEDLINE database for randomized clinical trials (RCTs) published in 1966–2009 supplemented by other electronic databases. Data were extracted from published RCTs of antipsychotic treatment in schizophrenia and schizoaffective disorder (SAD). This analysis, placebo response in short-term treatment (two to 12 weeks) was defined as mean change from baseline in BPRS total score (derived from Positive and Negative Syndrome Scale (PANSS) in 11 studies). A meta-regression analysis was performed to identify influential moderators of placebo response. Patient-level analysis was conducted to identify additional predictors, based on data from one long-term trial and two identically-designed, short-term trials in the ziprasidone clinical trial database. We applied Growth Mixture Model (GMM) to identify classes of trajectory for the placebo response.

**Results:** A total of 1246 placebo-treated patients from 41 RCTs had valid BPRS total scores. Demographics included: weighted mean age 38 years, duration of illness 16 years and 77% male. The weighted mean baseline, endpoint and reduction in BPRS were, respectively, 48.58, 46.10 and -2.59 (95% CI -4.08, -1.09). The average effect size was 0.27 (-0.44, 0.11) and heterogeneous across studies (p<0.001). Meta-regression analysis showed that greater placebo response was associated with shorter trials (p=0.001), community hospital (or mixed) treatment settings (p=0.02), more recently published studies (1990–2009) (p<0.01) and higher baseline severity score (p<0.01). Analysis of patient-level PANSS total score in the ziprasidone long-term study, however, showed no improvement over a one-year period in the higher baseline PANSS subgroup using GMM. Analysis of the placebo arms in the two short-term ziprasidone trials showed placebo responses in SAD bipolar patients were significantly lower than in schizophrenia patients. In the long-term one-year trial, GMM identified four classes of placebo response patterns for PANSS total score: (1) immediate worsening class (15%) in which patients experienced exacerbation of symptoms and discontinued the trial within six weeks of placebo treatment; (2) gradual worsening class (19%); (3) delayed worsening class (31%) in which patients experienced no change in symptoms for about 16 weeks and gradual worsening thereafter; and (4) no change in symptoms over the one-year study period (35%).

**Conclusions:** Our findings suggest that treatment settings, trial duration, schizoaffective bipolar diagnosis and baseline level of symptom severity could influence the magnitude of placebo response.

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

**Literature References:**
2. Kemp AS, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophren Bull 2008;epub.

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Trial Level Meta-Analysis of Duloxetine Efficacy on Painful Physical Symptoms in Major Depressive Disorder for Patients with Clinically Significant Painful Physical Symptoms at Baseline

Susan G. Ball, Ph.D., Melissa E. Spann, Ph.D., Durisala Desaih, Ph.D., James M. Russell, M.D., Michael J. Robinson, M.D.

Eli Lilly and Company, Indianapolis, IN

**Background:** Patients with major depressive disorder (MDD) often experience painful physical symptoms (PPS)1 and these associated symptoms complicate the diagnosis and treatment of depression.2 Duloxetine, a re-uptake inhibitor of both serotonin and norepinephrine neurotransmitters, has demonstrated analgesic efficacy in preclinical studies of animal models of persistent pain and in clinical trials of patients with diabetic peripheral neuropathic pain, fibromyalgia, chronic lower back pain or osteoarthritis of the knee. PPS has also been a focus within the MDD clinical trial program. Given the heterogeneity of the clinical trial database with regard to the prevalence of patients with PPS, and the use of different dose regimens, a meta-analysis has been undertaken to provide an overview of the efficacy of duloxetine for PPS in patients with MDD who had clinically significant levels of PPS at baseline.

**Methods:** The MDD duloxetine database of acute, double-blind, placebo-controlled studies consists of 11 studies: the treatment for seven studies was duloxetine 60 mg once daily whereas four studies used non-60 mg doses (20 mg twice daily, 40 mg twice daily and 60 mg twice daily). Overall pain was assessed across studies using different assessment tools, the Visual Analogue Scale (VAS), the Brief Pain Inventory (BPI), and the Numerical Rating Scale (NRS). For each study, patients with clinically significant levels of pain at baseline (a VAS overall pain rating ≥30, an NRS score =3 or a BPI 24 hours average pain rating =3) were selected to determine the individual trial effect sizes on the pain outcome measure. The effect sizes were based on the main effect of treatment calculated from the mixed-model repeated measure (MMRM) analysis. An overall effect size was obtained from the average of individual trial effect sizes weighted by the number of patients within each specific study.

**Results:** In 60 mg trials, the effect sizes ranged from 0.21 (CI: 0.03, 0.39) to 0.44 (CI: 0.17, 0.72). The mean effect size for the 60 mg trials was 0.29 (CI: 0.06, 0.52). In non-60 mg trials, mean effect sizes varied from 0.04 (CI: -0.24, 0.33) to 0.43 (CI: 0.05, 0.81). The overall weighted effect size for non-60 mg trials was 0.13 (CI: -0.19, 0.45). Across the 11 studies, the weighted effect size was 0.26 (CI: 0.00, 0.51).

**Conclusions:** The results of this meta-analysis showed that duloxetine 60 mg once daily is effective in pain reduction for patients with MDD and clinically significant PPS.

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

**Literature References:**
**Session II–29**

**Divalproex Sodium (DVX) for the Treatment of Impulsivity and Aggression in Connecticut Prisons**

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1 University of Connecticut Health Center, Farmington, 2 University of California, Davis, Medical Center, Sacramento

**Background:** Aggressive and impulsive behavior continues to be one of the most serious concerns confronting correctional facilities. An effective intervention treating impulsive aggression during incarceration is paramount in order to increase success of reintegration for these inmates upon release. Divalproex sodium (DVX) is frequently used to treat impulsivity and aggression in inmates with or without bipolar disorder. We previously conducted a retrospective chart review evaluating the use and utility of DVX in Connecticut correctional facilities. This chart review showed significant clinical benefit of DVX (p < 0.05) when impulsive aggression is the target symptom. Clinical experience suggests that certain comorbidities such as psychiatric comorbidities or maladaptive substance use and certain risk factors such as history of violence might predict impulsivity and aggression. In the present sub analyses of the original chart review, we investigated if specific variables related to demographics, type of offense, and comorbidities predicted better response to DVX treatment when impulsive aggression is the target symptom.

**Methods:** Clinical charts of offenders treated with DVX (n=168; 118 male and 50 female charts) for one or more months were randomly selected for clinical outcome review and were divided into bipolar and nonbipolar groups. The nonbipolar group was further divided into subgroups based on clinical impression for DVX prescription. Demographics, type of offense, psychiatric and substance use history was obtained. Treatment outcomes were evaluated based on a set of standardized criteria. These criteria for clinical status were initially determined and agreed upon by the investigator and supervising psychiatrists.

**Results:** In the inmates without bipolar disorder (44.6%), DVX was mainly used to target impulsivity/aggression (14.3%) and mood liability (17.3%). The impulsivity/aggression subgroup was the only nonbipolar subgroup in which DVX yielded significant clinical benefit (p < 0.05). The sub analyses of this group showed that inmates benefited more from DVX use if they had comorbid maladaptive substance use or current or recent psychotic symptoms. Other psychiatric comorbidities, demographic variables or history of violence and the type of offense (violent or nonviolent) did not have an impact on clinical outcomes with DVX use in this group of inmates.

**Conclusions:** DVX might be a useful agent in the treatment of impulsivity/aggression in incarcerated patients, especially in patients with comorbid maladaptive substance use or psychosis. Significance of these findings will be discussed in the context of the neurobiology of aggression, maladaptive substance use, psychosis and known aspects of DVX pharmacology of DVX.

**Source of Funding:** Abbott Laboratories.

**Literature References:**


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**Session II–30**

**Effect of Adjunctive Aripiprazole on Domains of Functioning in Patients with Major Depressive Disorder: A Pooled Analysis of Three Clinical Trials**

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1 Bristol-Myers Squibb, Plainsboro, NJ, 2 University of Pittsburgh, PA, 3 Bristol-Myers Squibb, Wallingford, CT, 4 Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ

**Background:** This analysis evaluated the effect of aripiprazole adjunctive to antidepressant therapy (ADT) on individual domains of functioning in patients with major depressive disorder (MDD) who did not achieve an adequate response with ADT monotherapy.

**Methods:** Pooled data were analyzed from three methodologically similar, randomized, double-blind, placebo-controlled trials of aripiprazole for the treatment of MDD. 1-3 Patient functioning was assessed using the Sheehan Disability Scale (SDS). Mean and individual domain SDS scores were retrospectively categorized, at baseline (Week 8) and endpoint (Week 14), as mild (0–3), moderate (4–6), or severe (7–10) functional impairment. Changes in mean SDS scores and domain scores were compared, using ANCOVA, between patients randomized to six weeks of adjunctive aripiprazole or placebo. Shifts in the distribution of mean SDS scores and domain scores were evaluated, using a generalized estimating equation (GEE) proportional odds model, between adjunctive aripiprazole and placebo.

**Results:** Overall, 81% of patients who did not respond to ADT monotherapy experienced moderate-to-severe functional impairment at baseline (Week 8) according to mean SDS scores. Approximatly 80% of patients reported moderate-to-severe functional impairment in social and family life domains, compared with only 50% in the work/school domain. From Week 8 to 14, adjunctive aripiprazole produced significant improvement in mean SDS scores, and social and family domains. No difference in mean score change was observed for the work/school domain.

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<th>Adjunctive Placebo</th>
<th>Adjunctive Aripiprazole</th>
<th>p-Value</th>
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<tr>
<td>Work/School Domain</td>
<td>39</td>
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<td>0.337</td>
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Significantly more patients randomized to adjunctive aripiprazole shifted to an improved level of functioning for mean SDS scores, and social and family life domains. No difference in distributional shifts was observed between groups for the work/school domain.

**Conclusions:** As demonstrated by Week 8 SDS scores, patients who failed to achieve an adequate response with ADT monotherapy experienced marked overall functional impairment, particularly in social and family relationships. Adjunctive aripiprazole significantly improved social and family life domains of functioning and produced clinically favorable shifts in the distribution of patients with improved levels of functioning.

**Source of Funding:** Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.

**Literature References:**


Session II–31
Does Sponsorship Influence Dosing in Randomized Controlled Trials of Antidepressants for Major Depressive Disorder? A Meta-Analysis

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Objective: To determine whether there are differences in dosing between sponsor and non-sponsor antidepressants in randomized controlled trials (RCTs) for major depressive disorder (MDD) and if these differences impact efficacy results.

Methods: MEDLINE, PsycINFO and pharmaceutical industry website searches were performed to collect RCTs examining antidepressant treatment for major depressive disorder published from 1996–2007 that included sponsor/non-sponsor medication arms and reported mean final drug dosages. Antidepressant dosing guidelines were used to assign a “dose ratio” to each drug reflecting its dose compared to the standard minimum and maximum doses. Meta-analyses were used to compare dosing and efficacy data.

Results: Fifty-two trials with 12,242 patients were analyzed. On average, sponsor drugs were dosed 24% higher than non-sponsor drugs (U=939.5, p<0.001). In trials where efficacy of the sponsor drug was statistically superior to the non-sponsor, sponsor drugs were dosed 46% higher. Studies where sponsor drugs were dosed at least 20% higher showed higher response rates to the sponsor drug (OR 1.21, 95% CI=1.09-1.35, p<0.001) while those where sponsor drugs were dosed less than 20% higher did not (OR 1.09, 95% CI=0.96-1.25, p=0.19). Baseline depression severity, dropouts/adverse events and fixed versus flexible dosing strategies showed no consistent correlation with dosing and outcome.

Conclusions: Sponsor drugs are dosed higher than non-sponsor drugs in antidepressant RCTs, particularly in those that claim superiority of the sponsor drug and this is associated with better sponsor drug outcomes. We suggest that future trials always report mean final doses, consider using dosing strategies from independent bodies and include a brief discussion when there are large differences in dosing between comparator drugs.

Source of Funding: None.

Literature References:

Session II–32
Analysis of Baseline Characteristics of Major Depressive Disorder Patients Treated with Antidepressant Therapy: A Pooled Analysis of Three Studies

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Background: The aripiprazole major depressive disorder (MDD) clinical trial program provides a unique dataset that allows evaluation of baseline symptom characteristics in patients with at least one historic antidepressant therapy (ADT) failure and comparison among respondents and non-respondents in a prospective, eight-week trial of ADT monotherapy. Comparison of symptoms at Week 8 among ADT responders and non-responders may have value in choosing appropriate adjunctive therapy for MDD patients.

Methods: Data were pooled from three nearly identical studies of patients with major depressive disorder. During an eight-week prospective phase, patients with one to three historic ADT failures were treated per investigator choice with a selective serotonin reuptake inhibitor (SSRI) (escitalopram, fluoxetine, paroxetine, sertraline) or a serotonin norepinephrine reuptake inhibitor (SNRI) (venlafaxine XR) under standard dosing guidelines with adjunctive placebo. Baseline and Week 8 item scores from the 16-item Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR16) were analyzed using methods similar to those previously described by the Sequestred Treatment Alternatives to Relieve Depression (STAR*D) investigators to determine whether there was a difference in the symptom profile between responders to ADT therapy and non-responders who met the criteria for randomization into the double-blind phase (<50% reduction 17-item Hamilton Rating Scale for Depression (HAM-D17) total score from baseline to Week 8, HAMD-17 Total Score =14 and CGI-I =3 at Week 8). Comparisons were made using the Cochran-Mantel-Haenszel general association test.

Results: After eight weeks of ADT monotherapy, 824/1912 (43%) patients responded and 1088/1912 (57%) patients did not meet response criteria. Both groups of patients reported a similar baseline QIDS-SR16 symptom profile. The most common baseline symptom was feeling sad, reported by over 97% of all patients, followed by energy level (93.8% of responders, 92.5% of nonresponders), concentration/decision making (93.0% versus 96.0%), general interest (91.6% versus 93.7%) and sleeping during the night (90.5% versus 92.5%). The proportion of patients reporting these five common symptoms at baseline decreased after ADT monotherapy in responders (38.2%–73.3%), compared with nonresponders (84.3%–89.6%; p<0.001 for all five symptoms versus responders), but remained among the most common symptoms even after ADT in both groups. Although not one of the most common baseline symptoms, thoughts of death or suicide occurred in 50.2% of responders and 58.2% of nonresponders and decreased to 6.2% versus 37.4% (p<0.001), respectively, after ADT monotherapy.

Conclusions: Responders and non-responders reported the same pattern of symptoms at baseline. It is interesting that while the proportion of patients with suicidal ideation was similar, responders reported significantly lower rates at end point compared with non-responders.

Source of Funding: Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.

Literature References:
**Session II–33**

**Efficacy and Safety of Adjunctive Aripiprazole in Combination with Lamotrigine in a Long-Term Maintenance Study in Manic or Mixed Subjects with Bipolar I Disorder (CN138-392)**

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**Background:** Adjunctive aripiprazole has been shown to be effective short-term treatment for manic or mixed episodes associated with bipolar I disorder and as monotherapy in long-term maintenance of relapse prevention. This study evaluated the efficacy and safety of aripiprazole+lamotrigine (LTG) compared with placebo+LTG for maintenance therapy in bipolar I disorder patients with a recent manic or mixed episode stabilized with aripiprazole+LTG.

**Methods:** This study consisted of two phases, a single-blind stabilization phase (nine to 24 weeks) (Phase 1) and a double-blind relapse phase (52 weeks) (Phase 2). In Phase 1, patients were stabilized with single-blind aripiprazole (10–30 mg/day) plus lamotrigine (100–200 mg/day, open-label) and had to maintain stability (Youth Mania Rating Scale (YMRS) = 12 and Montgomery-Åsberg Depression Rating Scale (MADRS) = 12) for eight consecutive weeks with one exception allowed (YMRS and/or MADRS > 12), except for the second to the last and last visit. In Phase 2, patients were randomized to aripiprazole+LTG or placebo+LTG and followed up to 52 weeks. The primary outcome measure was the time from relapse to reinstallation of a manic or mixed episode. Safety and tolerability parameters were assessed, including incidence of treatment-emergent adverse events (TEAEs).

**Results:** A total of 787 patients entered Phase 1 and 351 (173 placebo+LTG, 178 aripiprazole+LTG) were randomized into Phase 2. The completion rate in Phase 2 was placebo+LTG 30.6% and aripiprazole+LTG 36.5%. Discontinuation rates for placebo+LTG and aripiprazole+LTG for adverse events were 6% and 9% respectively, and for lack of efficacy were 31% and 22% respectively. The primary outcome measure showed that the Kaplan-Meier relapse rate for manic/mixed episodes was 23% for placebo+LTG and 11% for aripiprazole+LTG (hazard ratio=0.55, 95% CI [0.296, 1.030]; p=0.058). TEAEs that occurred in =5% in either group were the following (placebo+LTG, aripiprazole+LTG): akathisia (6%, 11%); insomnia (12%, 7%); anxiety (4%, 7%); upper respiratory infection (8%, 7%); agitation (5%, 6%); headache (8%, 5%); back pain (3%, 5%); and urinary tract infection (6%, 3%). Mean weight change (SE) for placebo+LTG was -1.81 kg (0.48) and 0.43 kg (0.47) for aripiprazole+LTG patients (last observation carried forward (LOCF), p<0.001). Similar weight change profile was seen with the observed cases dataset.

**Conclusions:** The combination of aripiprazole+LTG showed a reduced manic/mixed relapse rate versus placebo+LTG that approached, but did not reach, statistical significance. No unexpected TEAEs occurred with respect to the profile each individual medication established as monotherapy in a maintenance setting. The overall relapse rate was lower than anticipated and reduced the statistical power of the study and precision of the treatment comparison estimates.

**Source of Funding:** Bristol-Myers Squibb and Otsuka Pharmaceuticals Co., Ltd.

**Literature References:**

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**Session II–34**

**Rapid Improvement in the Five-Item Positive and Negative Syndrome–Excited Component (PANSS–EC) Scale for Agitation with Inhaled Loxapine**

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**Objective:** To analyze the efficacy of inhaled loxapine (AZ-004) in treating agitation using the Positive and Negative Syndrome–Excited Component (PEC) scale in two Phase 3 clinical trials.

**Methods:** Each trial was randomized, double-blind and placebo-controlled. Loxapine was administered via inhalation using the Staccato® system, which delivers thermally generated drug aerosol with IV-like kinetics. Consenting male and female adults, meeting DSM-IV criteria for schizophrenia (344 patients) or bipolar I disorder (314 patients) and presenting with a relevant degree of agitation at baseline, were enrolled. Patients received a single inhalation of either 0 mg (placebo), 5 mg or 10 mg of loxapine in an in-clinic treatment facility. The primary efficacy endpoint was the change from baseline in PEC total score at two hours post-dose. Change from baseline for each of the five items comprising the PEC scale (hostility, uncooperativeness, excitement, poor impulse control, tension) was determined starting at 10 minutes post-dose. Patients were also analyzed by baseline PEC score (median split), and response rates for the higher and lower agitation populations were compared.

**Results:** In each trial, both 5 and 10 mg AZ-004 were significantly superior to placebo for total PEC score starting at the first assessment time (10 min). Each item of the PEC improved with treatment, starting at 10–20 minutes after dosing. On average, each item improved one to two units from baseline over the first two hours post-dose for both patient groups. The median PEC score at baseline was 17 across the two studies. For the 10 mg dose groups, there was, on average, an 8.3 (schizophrenia, SZ) and 8.5 (bipolar disorder, BD) unit improvement for patients <17 at baseline and an 8.9 (SZ) and 9.7 (BD) unit improvement for patients >17 at baseline.

**Conclusions:** Based on PEC total score, AZ-004 produced rapid and significant improvement in agitated patients with schizophrenia or bipolar disorder, starting at 10 minutes. The change in total PEC score observed with AZ-004 treatment derives from similar changes on each of the five PEC items assessed. AZ-004 reduces agitation equally well in patients with higher or lower levels of agitation at baseline.

**Source of Funding:** Alexza Pharmaceuticals.

**Literature References:**
Session II–35

Aripiprazole Partial Agonism at SHT2c: A Comparison of Weight Gain Associated with Adjunctive Aripiprazole to Antidepressants with High versus Low Serotonergic Activities

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Background: Antipsychotic medications are associated with an increased risk of weight gain. A proposed mechanism is the antagonism of the SHT2c receptor, which has been associated with an increase in food intake. In contrast, agonism of the SHT2c receptor, as produced by fenfluramine and M-chlorophenyl-piperazine, may lead to suppression of appetite. Furthermore, Tecott and colleagues developed a strain of mice lacking the gene for the SHT2c receptor. These mice demonstrated increased obesity. In long-term studies in schizophrenia and bipolar disorder, aripiprazole treatment has not been associated with a mean increase in body weight. However, in a study where aripiprazole was used as an adjunct to antidepressant therapy for major depressive disorder, weight gain (1.7 kg) was significantly higher than placebo (0.4 kg). Several studies demonstrate that aripiprazole is a partial agonist at SHT2c. Aripiprazole may be an agonist in environments with low SHT2c stimulation and an antagonist in conditions of high SHT2c stimulation. In the presence of antidepressants with high serotonergic activity, aripiprazole may act as an antagonist of the SHT2c receptor, thus increasing the potential for weight gain. In environments with low serotonergic activity, aripiprazole may act as an agonist of the SHT2c receptor, thus having less effect on the potential for weight gain. This may explain why aripiprazole has not been associated with significant weight gain in previous studies focusing on schizophrenia and bipolar disorder.

Methods: A review of the electronic medical record at the VISN 22 Veterans Affairs database from January 1, 2003 thru December 1, 2009, was performed after institutional review board (IRB) approval comparing patients’ weights and body mass indexes (BMIs) on aripiprazole monotherapy, on aripiprazole plus a high serotonergic antidepressant (citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine), and on aripiprazole plus a low serotonergic antidepressant (bupropion) for a minimum duration of six months.

Results: Overall, patients on monotherapy with aripiprazole (N=429) lost an average of 0.68 pounds. Patients on the combination of aripiprazole and a high serotonergic antidepressant (N=112) gained an average of 3.87 pounds. Patients on the combination aripiprazole and a low serotonergic antidepressant (N=19) lost an average of 4.96 pounds.

Conclusions: Aripiprazole’s partial agonism of the SHT2c receptor may explain the increased weight gain found in studies where aripiprazole is used as adjunct treatment to antidepressants.

Source of Funding: None.

Literature References:

Session II–36

Improvements in Cognitive Functioning during Inpatient Hospitalization for Unipolar and Bipolar Depression with and without Psychotic Features

Caleb Siefert, Ph.D., John Matthews, M.D., Adrienne van Nieuwenhuizen, B.A., Rita Seabrook, B.A., Lauren House, M.A., Kaloyan Tanev, M.D., David Abramson, M.D., Maurizio Fava, M.D.
Massachusetts General Hospital, Boston

Introduction: Several studies have demonstrated cognitive impairment in patients with mood disorders during the acute phase. However, less is known about the course of cognitive functioning with treatment, particularly with regards to the presence of psychotic symptoms. Our objectives were to: (1) examine the response of cognitive functioning over the course of inpatient treatment of patients with major depressive disorder or bipolar disorder, depressed type with and without psychotic features; (2) determine the impact of psychosis on cognitive functioning pre and post treatment.

Methods: Subjects included 39 patients admitted to an inpatient unit at Massachusetts General Hospital. All participants met DSM-IV criteria for major depressive disorder or bipolar disorder, depressed type, with or without psychotic features based on Structured Interview for DSM Disorders–patient edition (SCID-I/P) interview. Severity of depression and psychosis were determined by the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and Brief Psychiatric Rating Scale (BPRS) respectively. Neuropsychological evaluations were determined by a battery of assessments.

Results: Pre-post analysis indicated that this cohort of patients experienced significant improvement in depression over the course of treatment (pre mean =24.00 ± 5.84, post mean =11.54 ± 6.82; paired t = -7.76, p<0.001) as measured by the HAM-D-17. Paired t-tests revealed that patients also experienced significant improvement from pre-to-post on tasks of executive functioning (paired t =2.31, p=0.04), memory (paired t =5.47, p<0.01) and psychomotor functioning (paired t =3.05, p=0.01); however, there were no significant improvements in attention or visuospatial scores. Additional post-hoc analyses compared differences in cognitive functioning at time of admission across individuals with and without psychotic features. Higher scores on the BPRS on admission were associated with significantly lower scores for executive function (n=0.52, p=0.01), memory (n=0.49, p=0.02) and attention (n=0.50, p=0.059), after controlling for HAM-D-17 scores. These relationships were no longer significant post treatment. This pilot study was funded by a private donation.

Conclusions: There was a corresponding improvement in executive functioning, memory, and psychomotor speed with improvement in depression. Psychotic features predicted significantly lower scores for executive function, memory, and attention at baseline, but did not predict cognitive functioning post treatment.

Source of Funding: Departmental funds.

Literature References:
**Session II–37**

**Assessment of Spontaneous and Evoked Gamma Oscillations by Quantified Electroencephalogram (EEG), A Potential Biomarker of Glutamatergic Transmission: Methodological Issues in Humans, Descriptive Data and Test-Retest Reliability**

Remy Luthringer, Ph.D.,1 Jim Fergusson,2 Peter Boeijinga,2 Nathalie Pross,2 Corinne Stater,1 Laurenten Taintz,2 Damien Maurice,1 Geoffrey Viardot,2 Philippe Danjou1

1FORENAP Pharma, Rouffach, France, 2FORENAP, Research and Development, Rouffach, France

**Background:** The gamma band (30–70Hz) of the electroencephalogram (EEG) is a domain of growing interest for many areas, as a potential biomarker in schizophrenia or Alzheimer’s disease. More generally it is a read of synchronization mechanisms (binding) between distant neuronal populations. These are involved in all sensory and cognitive tasks and could also be a potential biomarker for new chemical entities when measured either in static (resting) or dynamic (evoked or induced) conditions. Optimal setting is not known. The non-competitive NMDA antagonist ketamine in rodents produces a robust increase in resting gamma while due to the paradoxically sparse qEEG data available in humans, at subanaesthetic levels, the relative magnitude of spontaneously recorded gamma would have to be calibrated versus the more documented evoked responses triggered either by auditory or visual stimuli. Reliability of auditory stimulation has been established but since the visual modality was preferred it remained to be established. This study was therefore the first step to assess the normative values of spontaneous and visually-evoked gamma and their test-retest reliability in healthy subjects as a first validation step of a glutamatergic sensitive biomarker.

**Methods:** Quantified EEG was recorded with silver/silver electrodes: 28 on the scalp, according to the 10/20 system with linked earlobes as a reference and four for the purpose of electrooculogram in order to closely monitor eye movements. A Grass system with a sampling rate of 400 Hz was used. Low and high pass filters were set to 70 Hz and 0.3 Hz and a notch filter to 50 Hz. On each session there were three minutes of recording and eyes closed and three minutes eyes open, then followed by the stimulus presentation, eyes open. Evoked gamma band response was triggered by the method described by Schadov with 50% of contrast between gratings of visual targets either with vertical lines (25 infrequent stimuli) or horizontal lines (100 frequent stimuli). The presentation lasted 1000 ms and the inter-stimulus interval was 1600 to 2400 ms. The visual stimuli were presented on a 22”LCD monitor using the E-prime software. After scanning, the subjects were recorded on two distinct occasions separated by at least 24 hours.

**Results:** Twelve healthy subjects were enrolled seven males and five females (22–54 years) and scanned in the two periods. None dropped out and EEG data was analyzed after manual rejection of artefacts. Sample size reassessment after analysis of this first set may lead to increased sample size.

**Source of Funding:** FORENAP Pharma

**Literature References:**

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**Session II–38**

**Partial Response to Antidepressant Monotherapy Predicts Remission: Results from the Aripiprazole Clinical Trial Program in Major Depressive Disorder**

Michael E. Thase, M.D.,1 J. Craig Nelson, M.D.,2 Stephen R. Wisniewski, Ph.D.,3 Ross A. Baker, M.D., M.B.A.,4 Linda D. Rollin, Ph.D.,1 Robert D. McQuade, Ph.D.,1 Robert M. Berman, M.D.1

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**Background:** The aripiprazole major depressive disorder (MDD) clinical trial program proved a unique data set of both partial and non-responders that are evaluated in a group of patients with a documented history of one to three antidepressant therapy (ADT) failures. As remission is the goal of therapy, our objective was to determine which patient characteristics might be predictive of remission, regardless of combination or monotherapy treatment.

**Methods:** Two data sets were evaluated, pooled data from two registrational studies, and data from a third nearly identical study. Remission was defined as a Montgomery-Asberg Depression Rating Scale (MADRS) total score of 10 (and a 50% decrease in MADRS total score). A univariate logistic regression model was used to test for significant predictors of remission. Categorical variables included in the model were sex; age (46 years/younger); race (white/non-white); number of previous depressive episodes (two or three episodes versus zero or one and also four episodes versus zero or one); number of adequate ADT trials prior to study entry (zero to one versus two or more); ADT (escitalopram as the reference compared with fluoxetine, paroxetine, sertraline or venlafaxine); and minimal (zero to 25% decrease in MADRS total score) response to eight-week prospective, double-blind period of ADT monotherapy. Multivariate analysis also was conducted to control for potential correlations among the variables.

**Results:** Partial ADT responders (n=129) were more than twice as likely as minimal responders (n=239) to remit with aripiprazole augmentation (OR=2.09, p=0.0026, 95% CI=1.29 to 3.38). Partial ADT responders (n=94) also were more likely to remit than minimal responders (n=262) with placebo augmentation (OR=4.44, p=0.0001, 95% CI=2.44 to 8.06). None of the other categorical variables were significantly associated with remission. Multivariate analysis produced similar results. Separate analysis of the third study showed similar results for aripiprazole, however placebo partial responders were not significantly more likely to achieve remission than minimal responders using either univariate or multivariate regression models.

**Conclusions:** Partial responders to ADT monotherapy are more likely than those with minimal response to achieve remission during ADT augmentation with aripiprazole or placebo. History of depressive episodes and prior treatment failure were not significant predictors of remission. Partial response to an eight-week prospective period of ADT monotherapy was a significant predictor of remission; ongoing analyses may identify symptom clusters that differentiate remission after augmentation with aripiprazole versus placebo.

**Source of Funding:** Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.

**Literature References:**
Session II–39

Rater Training on Hamilton Rating Scale for Depression (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS) and Youth Mania Rating Scale (YMRS)—What Were the Difficult Items to Rate?

Richa Gaur, Ph.D.1, Martha Sajatovic, M.D.2, Nathan Lee, M.Sc.3, Luis Ramirez, M.D.4, Geetika Nath, M.A.1, Hossein Kaviani, Ph.D.1

1The Cognition Group, Gurogan, Haryana, India, 2Case Western Reserve University, Cleveland, OH, 3The Cognition Group, Dartfort, Kent, UK, 4Quality Outcomes Training, Cleveland, OH

Introduction: Training of raters on pre-set rating conventions is critical to increase the reliability of ratings in central nervous system (CNS) drug trials. Identification of items anticipated to be most challenging for raters to assess in order to optimize rater training programs. This study examined raters’ ratings provided in an online rater training program on the Hamilton Rating Scale for Depression (HAM-D), Montgomery-Åsberg Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) for a bipolar depression trial.

Methods: One hundred-ninety-four raters from 16 countries, 80 sites, speaking 20 different languages, with clinical experience in bipolar disorder ranging from zero to 40 years participated in an online (via website) rater training and certification program. The website included learning modules on HAMD, MADRS and YMRS with an integration of visual learning materials and nine videos of three bipolar patients interviewed by two American clinicians on these three scales. Raters viewed and rated the videos on HAMD, MADRS and YMRS, ratings were entered online and analyzed for consistency and variability compared with gold consensus ratings (GCRs) achieved by three experts raters. Inter-rater agreement was assessed using Kappa statistics. Ratings between the raters and the GCRs for the individual scale items were assessed using McNemar test for binomial proportions.

Results: No significant difference for raters was found among countries, raters’ past experience on bipolar disorder or previous training on HAMD, MADRS and YMRS. Inter-rater agreement for the three videos on the scales ranged from substantial to moderate (HAM-D, Kappa = 0.72, 65 and 0.43, p<0.001), (MADRS, Kappa =0.65, 0.47 & 0.44, p<0.001), (YMRS, Kappa =0.75, 0.64 and 0.54, p<0.001). The McNemar results showed that HAMD =8/17, 4/17 and 7/17, MADRS =9/10, 9/10 & 5/10) and YMRS =3/11, 5/11 and 5/11 individual items were significantly different than GCRs. The mood disorder rating scale items found to be difficult to rate on all patient videos included sleep (insomnia early & late). On the HAMD, anxiety and retardation were most difficult, while most difficult items on the MADRS were apparent sadness, inner tension, concentration, lassitude and inability to feel. Most difficult items for the YMRS were irritability, language/thought disorder, content, disruptive/aggressive behavior and appearance.

Conclusions: While overall substantial to moderate agreement was achieved for raters across countries in rating mood disorder rating scales, the MADRS appeared to be the more difficult scale to rate compared to HAMD and YMRS. Rater training and preparation for randomized controlled trials (RCTs) in mood disorder treatments should include focused training on the assessment of sleep/insomnia as well as specific measures unique to the HAMD, MADRS and YMRS.

Source of Funding: The Cognition Group.

Literature References:

Session II–40

Associations between Child Behavior Checklist Profiles and Candidate Genes in Adolescent Bipolar Disorder

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1Stanford University School of Medicine, Emerlad Hills, CA, 2University of California, Los Angeles, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, 3University of Colorado, Boulder

Introduction: Although family and twin studies have implicated genetic factors in the etiology of bipolar disorder, few studies have examined associations between candidate genes and bipolar disorder in children and adolescents. This project investigated the phenomenology of bipolar disorder in children and adolescents by examining relationships between Child Behavior Checklist (CBCL) symptom profiles, DSM-IV bipolar diagnoses and four candidate genes in cases and controls. We hypothesized that the CBCL juvenile bipolar disorder (JBD) and externalizing (EXT) profiles would be associated with bipolar diagnoses and candidate genes.

Methods: Ninety adolescents diagnosed with bipolar disorder were compared with 270 ethnicity- and sex-matched controls on measures of affective symptomatology and candidate genes.

Results: CBCL-JBD profiles efficiently discriminated cases from controls. The long DAT1 allele and the short SHTLPR allele were associated with JBD profiles as assessed by the CBCL. Finally, the short DRD4 allele was associated with depression in older bipolar cases.

Discussion: Contributing genes are likely numerous and of small effect, but identifying genetic risk profiles for bipolar disorder may illuminate the relationship between adult bipolar disorder and its adolescent-onset counterpart. Genome-wide association and gene-environment interaction studies may inform understanding of the complicated genetic underpinnings of child and adolescent bipolar disorder.

Source of Funding: National Institute of Mental Health (R01MH073871, R34MH077856).

Literature References:
Session II-41

Ratings of Manic Psychopathology in Geriatric Bipolar Patients: An Acute Pharmacotherapy of Late-Life Mania (Geri-BD) Report

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1Weill Medical College of Cornell University, White Plains, NY, 1Case Western Reserve University and Cleveland Clinic, Cleveland, OH, 2University of Pittsburgh, PA, 3Toronto General Hospital, Toronto, Ontario, Canada, 2University of Pennsylvania, Philadelphia, 2Duke University, Durham, NC, 4Baylor College of Medicine, Houston, TX, 4National Institute of Mental Health, Bethesda, MD

Background: While bipolar manic states are not uncommon among elders treated at psychiatric services, the evidence-base regarding signs and symptoms in these patients is limited. Early reports have suggested that their psychopathological features may be associated with age, sex, cognitive performance and medical comorbidity. We therefore examined correlates of standardized mania ratings in initial participants in a multicenter study of geriatric bipolar patients.

Methods: The subjects studied were the first (n=100) randomized participants in an NIH-funded multicenter study of pharmacotherapy of bipolar disorder in elders (the Acute Pharmacotherapy of Late-Life Mania [Geri-BD]). They were aged >60 years and had a diagnosis of bipolar I disorder manic, hypomanic or mixed. They lacked a diagnosis of dementia, were medically stable, did not have concomitant pathology to lithium or valproate treatment and they gave written informed consent. At baseline, manic psychopathology was assessed using the Young Mania Rating Scale (YMRS), while depression assessment included the Hamilton Rating Scale for Depression–17-item (HAM-D-17). Documentation of cognitive performance included the Mini-Mental State Examination (MMSE). Medical burden was rated with the Cumulative Illness Rating Scale–Geriatric (CIRS-G).

Results: The mean age of the subjects (n=100) was 68.9 years (SD=7.1 years). Half were female. The mean YMRS total score was 26.4 (6.7). Total YMRS scores were not associated with age, sex or MMSE. Older age was associated with abnormal (higher) scores on the YMRS Insight item (r=0.33, p<0.001). Males had higher scores on the sexual interest and sleep items (t=2.24, p<0.03; t=2.91, p<0.004, respectively). Higher total HAMD-17 scores were associated with lower scores on the mood, activity-energy and insight items (r=-0.35, p<0.001; r=-0.22, p<0.03; r=-0.21, p<0.04) but higher scores on the irritability and disruptive-aggressive behavior items (r=0.35, p<0.001; r=0.20, p<0.05). Lower MMSE scores were associated with higher scores on the language-thought disorder, disruptive-aggressive behavior and insight items (r=0.34, p<0.001; r=0.26, p<0.01; r=0.38, p<0.001; and r=0.23, p<0.03). Higher (more abnormal) total CIRS-G scores were associated with higher YMRS total scores, and with higher scores on the language-thought disorder, disruptive-aggressive behavior and insight items (r=0.34, p<0.001; r=0.26, p<0.01; r=0.38, p<0.001; and r=0.23, p<0.03). Higher (more abnormal) total CIRS-G scores were associated with higher YMRS total scores, and with higher scores on the language-thought disorder, disruptive-aggressive behavior and insight items (r=0.34, p<0.001; r=0.26, p<0.01; r=0.38, p<0.001; and r=0.23, p<0.03).

Conclusions: These preliminary findings suggest that in manic bipolar elders, YMRS item ratings are associated with demographic and other clinical features. Further studies of standardized assessments of manic psychopathology in this population are warranted; these can include examination of differences from young manic patients, and exploration of individual profiles as predictors of differences in outcomes of treatments.

Source of Funding: National Institute of Mental Health (U01 MH068847; K02 MH06028).

Literature References:

Session II-42

Conversion of Lisdexamfetamine Dimesylate to Active d-Amphetamine

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Background: Lisdexamfetamine dimesylate (LDX, Vyvanse®), a long-acting prodrug stimulant, requires conversion to d-amphetamine (d-amp) for therapeutic activity. LDX is absorbed throughout the intestines, likely by transporter-mediated uptake. However, a candidate transporter, human peptide transporter-1 (hPEPPT1), is not highly expressed in the large intestines. Conversion of LDX to d-amp occurs primarily in the blood, specifically red blood cells (RBCs). These in vitro studies examine potential conversion by contents of the large intestines and potential conversion in blood-containing pathologically deformed RBCs.

Methods: In separate studies, fresh cecum contents from three male rats and colostomy specimens from two human donors were diluted with 0.1 M potassium phosphate buffer (pH=7.4). Incubations up to four hours with LDX (1 μg/mL) at 37°C under N2 stream were performed. Fresh blood samples from two human male donors with sickle cell disease and two healthy control donors were incubated for up to four hours with LDX (1 μg/mL) at 37°C. LDX and d-amp were measured by a validated LC/MS/MS method.

Results: LDX concentrations declined over time with rat cecum contents; after four hours, 7.2% of initial LDX remained. Mean d-amp levels rose concurrently (62.1 to 2735.1 ng/mL at zero and four hours, respectively). Control incubations containing LDX and buffer showed no decline in LDX and no increase in d-amp. No decline in LDX and increase in d-amp were observed with human colostomy specimens. In incubations of blood from the two donors with sickle cell disease, LDX concentrations declined over time with 14.1% and 15.3% of initial LDX remaining after four hours. Similarly, in incubations of blood from two healthy donors, LDX concentrations declined over time with 13.1% and 10.5% of initial LDX remaining. Half-lives of LDX disappearance were 1.30 and 1.36 hours for the donors with sickle cell disease and 1.15 and 1.13 hours for the healthy donors. In blood samples from donors with sickle cell disease and healthy controls, d-amp concentrations rose similarly.

Conclusions: Conversion of LDX occurred with rat cecum contents but not with human colostomy specimens. Any unabsorbed LDX reaching the large intestines may therefore remain intact and be available for absorption by a different transporter to hPEPPT1. Delivery of active d-amp from LDX is similar in subjects with or without sickle cell disease.

Source of Funding: Shire Development, Inc.

Literature References:
Session II–43

**Indoleamine-Dioxygenase Activity is Associated with Psychiatric and Clinical Outcomes in Patients with Coronary Artery Disease**


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**Background:** We have previously observed an association between depressive symptoms and an increase in inflammation-stimulated synthesis of kynurenine (K) from tryptophan (T) by indoleamine 2,3-dioxygenase (IDO) in a cohort of patients with coronary artery disease (CAD). 1 In cross-sectional investigations, we have observed associations of both K/T ratios 1 and depressive symptoms 1 with cardiopulmonary fitness. Depressive symptoms 1 and cardiopulmonary fitness 2 are important predictors of mortality in this population, which may be interrelated through inflammatory activation. However, the significance of the K/T ratio in psychiatric and medical prognoses and has not been evaluated.

**Methods:** Subjects with CAD (n=37) were followed prospectively over a one-year cardiac rehabilitation (CR) program. Demographic, anthropometric and cardiac data were obtained by chart review. The presence of a major depressive episode or minor depression was assessed in a structured clinical interview for DSM-IV criteria at baseline and at completion of CR. Kynurenine and tryptophan were assayed from fasting plasma samples at completion of CR to obtain the K/T ratio. A standardized exercise stress test was administered to assess cardiopulmonary fitness.

**Results:** Eight subjects met criteria for depression at entry into CR and remained depressed after one year of CR (four major depression; four minor depression). Higher K/T ratios after one year of CR (50.3±39.0 versus 30.4±10.2 µmol/mmol) were significantly associated with depression after one year (ß=0.456, p<0.006) in linear regression controlling for age and time since most recent acute coronary syndrome (tACS). Higher K/T ratios after one year were significantly associated with poorer cardiopulmonary fitness outcome (ß=0.313, p=0.026) in linear regression controlling for age and tACS.

**Conclusions:** IDO activation was associated with depression and with poorer clinical outcome in subjects with CAD after one year of CR. Continuation of recruitment is warranted in order to control for important clinical confounders such as CAD severity. Further study might qualify the utility of the K/T ratio as a biomarker or inform clinical trials based on the involvement of the kynurenine pathway in depressed patients with CAD.

**Source of Funding:** Heart and Stroke Foundation (NAS857 and T6383), Physicians' Services Incorporated Foundation, Drummond Foundation (2006 RFA6).

**Literature References:**

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Session II–44

**Effect of Language-Specific Training on Rater Performance in Assessment of Positive and Negative Syndrome Scale (PANSS) Items and Subscales**

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**ProPhase LLC, NY**

**Background:** Although globalization of central nervous system (CNS) clinical trials requires assessments to be carried out in dozens of languages across the globe, the standard method of training investigators and monitoring their performance continues to be monolingual. This causes biases, particularly when attempting to translate key concepts in multilingual forums. Monolingual training materials and methods may dramatically affect the assessment of inter-rater reliability. There is a concerted need for culturally adequate training materials developed in the relevant languages spoken by investigators. Prior evidence suggests this will increase the quality of investigator's training and monitoring and ultimately lead to more efficient studies and relevant findings.

**Methods:** Data were pooled from a series of training programs for the Positive and Negative Syndrome Scale (PANSS), including English and Russian-language materials. A total of 111 investigators and raters were included. Investigators' performance was compared between multiple groups, including: (1) those with significant prior experience (two years or more); and (2) those with limited or no prior experience using the PANSS. Results from four videos, including two filmed in English with subtitles or translated transcripts were compared with performance on two videos filmed entirely in Russian (i.e., with Russian-speaking interviewers and subjects). Agreement versus gold-standard scores was calculated within each group of raters for each video, taking experience level and language into account, F-tests were conducted on within-sample variance, and standardized measures of internal consistency (ICC) were also taken.

**Results:** Within the group of participants with less experience, the average level of agreement with gold standard was relatively low as compared to more experienced raters for both English and Russian-language videos (p=0.01). Negative symptoms demonstrated the lowest scores on measures of agreement (p<0.05) and internal consistency, but continued to demonstrate significant differences when Russian-language materials were utilized, regardless of rater prior experience. Reliability on a subset of items nested within the general psychopathology subscale may be affected by linguistic or cultural factors.

**Conclusions:** The results of this study confirms that assessment in negative symptoms can be improved through the use of professional, adapted and standardized materials in native languages for global investigators. While experience and prior training does affect overall performance, the differences shown in assessment of negative symptoms and subsets of symptoms from the general psychopathology scale persists across language groups. Further training and research on negative symptoms and non-verbal items in multi-national trials and further research should be carried out.

**Source of Funding:** ProPhase LLC.

**Literature References:**
Efficacy of Lurasidone in Schizophrenia: Summary of Results from the Clinical Development Program

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Objective: Lurasidone is a novel compound currently under development for the treatment of schizophrenia. The aim of this analysis is to provide an overview of the four available Phase 2/3 placebo-controlled trials demonstrating efficacy in patients with schizophrenia.

Methods: In all four studies (D10500006; D1050196; D1050229 (Pearl 1); D1050231 (Pearl 2)) subjects meeting DSM-IV criteria for schizophrenia with an acute exacerbation were randomized to fixed doses (40 mg, 80 mg or 120 mg) of double-blind lurasidone (LUR) for six weeks. The primary efficacy outcome was change in the Brief Psychiatric Rating Scale (BPRS; 006; 196) and change in Positive and Negative Syndrome Scale (PANSS) total score (Pearl 1; Pearl 2). Secondary measures included Clinical Global Impressions Scale–Severity (CGI-S) and PANSS positive and negative symptom subscales.

Results: In study 006, treatment with LUR-40 and LUR-120, respectively, was significantly superior to placebo on the BPRS (p=0.018; p=0.004), and on the CGI-S (p=0.002; p=0.001). In study 196, treatment with LUR-80 was significantly superior to placebo on the BPRS (p=0.012) and on secondary measures—PANSS total (p=0.004), and positive (p=0.006) and negative (p=0.025) subscale scores; and on the CGI-S (p=0.007). In Pearl 1, treatment with LUR-80 was significantly superior to placebo on the PANSS total and CGI-S, respectively (p=0.011; p=0.005), but these assessments were not significant for LUR-40 or LUR-120. In Pearl 2, treatment with LUR-40 and LUR-120, respectively, were significantly superior to placebo on the PANSS total score (p<0.001; p=0.011) and on secondary measures—PANSS positive (p=0.018; p=0.035) and negative (p=0.002; p=0.045) subscale scores; and on the CGI-S (p=0.006; p=0.040).

Conclusions: Lurasidone has demonstrated efficacy in four placebo-controlled trials in patients with acute schizophrenia, for both primary and secondary outcome measures. Lurasidone fixed doses of 40, 80 and 120 mg have each shown efficacy at the primary study endpoint in two studies, providing replicated evidence of efficacy for each dose.

Source of Funding: Dainippon Sumitomo Pharma.

Pooled Analysis of the Efficacy of Desvenlafaxine 50 mg Compared with Placebo in the Patients with Moderate or Severe Major Depressive Disorder

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Objective: To characterize the efficacy of the serotonin norepinephrine reuptake inhibitor (SNRI) desvenlafaxine (administered as desvenlafaxine succinate) in patients with moderate or severe major depressive disorder (MDD).

Methods: Data from three double-blind, fixed-dose studies1,2,3 in outpatients with Diagnostic and Statistical Manual of Mental Disorders (DSM) defined MDD were pooled. Patients were randomly assigned desvenlafaxine 50 or 100 mg/d or placebo; this report summarizes findings with 50 mg/d. The primary end point was improvement in 17-item Hamilton Rating Scale for Depression (HAMD-17) scores from baseline in patients with moderate (HAMD-17=25) or severe (HAMD-17=25) MDD. Secondary outcomes included the percentage of patients who achieved response (=50% reduction in HAMD-17), remission (HAMD-17=7), and improvement in total scores of the Clinical Global Impression-Improvement (CGI-I), Sheehan Disability Scale (SDS), Covi Anxiety (COVI), and World Health Organization Well-being Index (WHO-S). Changes from baseline in scores were evaluated using analysis of covariance. Fisher’s exact test compared response and remission values. Tolerability assessments included treatment-emergent adverse events (TEAEs), discontinuation due to adverse events (AEs), and taper/poststudy-emergent AEs.

Results: This analysis included 933 patients (moderate on desvenlafaxine 50 mg=294; severe on desvenlafaxine 50 mg=168). Desvenlafaxine improved HAMD-17 scores versus placebo in patients with moderate (difference adjusted means [95% CL]) = (1.82 [3.10, 0.55]; p=0.003), and severe MDD ((1.89 [3.75, 0.03]; p=0.046). Desvenlafaxine significantly improved CGI-I (p=0.003), SDS (p=0.001), COVI (p=0.014) and WHO-S (p=0.001) scores versus placebo in moderately depressed patients. A greater percentage of desvenlafaxine-treated patients with moderate MDD achieved remission (35% versus 28%; p=0.044) or response (53% versus 47%, respectively; p=0.05) versus placebo. Secondary outcomes in severely depressed patients did not differ significantly. TEAEs reported by =5% of desvenlafaxine-treated patients were nausea, dizziness, insomnia, hyperhidrosis, constipation, fatigue and decreased appetite. Rates of discontinuation due to AEs were 4.5% for desvenlafaxine 50 mg/d and 4% for placebo. Taper/poststudy-emergent AEs reported by =5% of desvenlafaxine patients were dizziness, nausea and drug withdrawal syndrome.

Conclusions: Desvenlafaxine 50 mg/d significantly improved depressive symptoms in patients with moderate or severe MDD.

Source of Funding: Pfizer, Inc.


Session II–47

Milnacipran Improves Pain, Patient Global Impression of Change (PGIC), Physical Function and Depressive Symptoms in Fibromyalgia: Results from a Placebo-Controlled Milnacipran Trial

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Background: The management of fibromyalgia (FM) is complicated by multiple symptoms, including pain, fatigue, stiffness, physical dysfunction and depressive symptoms. Similar to previous trials of milnacipran, this trial assessed the efficacy of milnacipran 100 mg/day using composite responder analyses to identify individual patients who simultaneously experienced clinically meaningful improvements in multiple FM symptoms.

Methods: FM patients were randomized to milnacipran 100 mg/day (n=516) or placebo (n=509) for 12 weeks of stable-dose treatment. Primary endpoints included two composite responder analyses. A two-measure analysis required individual patients to have =30% improvement from baseline in pain VAS scores and a rating of “much improved” or “very much improved” on the Patient Global Impression of Change (PGIC); a three-measure analysis also required a =6-point improvement in the SF-36 Physical Component Summary score. Depressive symptoms were assessed by using the Beck Depression Inventory (BDI).

Results: Treatment with milnacipran versus placebo resulted in a significantly higher proportion of composite responders (two-measure: 42% versus 26%; three-measure 30% versus 16%; both p<0.001). At endpoint, LS mean improvements from baseline in BDI scores were significantly greater with milnacipran versus placebo (-2.12 versus -1.24; p=0.008). In a post-hoc analysis, small but statistically significant correlations were found between changes in BDI in the milnacipran group and changes in pain VAS (r=0.210) and PGIC (r=0.309) (both p<0.001). However, pain and PGIC improved regardless of changes in BDI. The most common adverse event was nausea.

Conclusions: In FM patients, treatment with milnacipran 100 mg/day significantly improved multiple domains, including pain, global status, physical function and depressive symptoms.

Source of Funding: Forest Laboratories, Inc. and Cypress Bioscience, Inc.

Literature References:


Session II–48

Post-Hoc Endpoint Readjudication of the Secondary Sudden Death Endpoint per International Classification of Diseases (ICD) 10 Coding in the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) Trial

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Background: The results of the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) trial,1 comparing the cardiovascular safety of ziprasidone and olanzapine, have been previously reported.2 This large simple trial compared the risk of non-suicide death associated with ziprasidone versus olanzapine in real-world use. Following the initial submission of the results, the Food and Drug Administration (FDA) requested an additional analysis with a readjudication using International Classification of Diseases (ICD) 10 coding guidelines of the secondary outcome of sudden death.

Methods: A post-hoc readjudication of all fatal events for the secondary endpoint of sudden death was conducted using ICD 10 coding criteria for sudden cardiac death (I46.1) and sudden death not otherwise specified (R96.0 and R96.1). A sensitivity analysis of this post hoc analysis was also conducted incorporating unattended or ill-defined causes of death (R98 and R99). An additional supplemental sensitivity analysis was conducted to capture cases which might fall outside of the restrictive ICD 10 coding schema. Analyses included treatment comparisons for the one-year incidence of mortality by estimating relative risks (ziprasidone incidence/olanzapine incidence) and the corresponding 95% confidence intervals (CIs). The two-tailed significance level was p<0.05. All tests were performed with “SAS, version 9.1.3”.

Results: Data from the post-hoc readjudication of sudden death were consistent with the study’s initial findings. There was no statistically significant difference in one-year incidence of mortality between ziprasidone and olanzapine for Sudden Death not otherwise specified and Sudden Cardiac Death (ICD 10 Codes R96.0 or R96.1 or I46.1) (relative risk =1.11, 95% CI: 0.45, 2.77). The sensitivity analysis incorporating unattended or ill-defined causes of death (R98 and R99) yielded a similar result (relative risk=0.73, 95% CI: 0.44, 1.22). Further, the supplemental sensitivity analysis resulted in a risk ratio of 0.99 (95% CI: 0.65, 1.50). The results from the analysis of mortality rates based on person-time on assigned treatment were consistent with the results from the analysis of one-year incidence of mortality.

Conclusions: ZODIAC is the largest randomized study of patients with schizophrenia conducted to date. This large study did not detect an increased risk of non-suicide death associated with the use of ziprasidone versus olanzapine. There was a statistically significant difference in the risk of sudden death comparing persons randomized to ziprasidone versus olanzapine across all readjudicated endpoints.

Source of Funding: Pfizer, Inc.

Literature References:

Altered Somatostatin (SST) and Nerve Growth Factor Inducible (VGF) Gene Expression in Anterior Cingulate Cortex of Post-Mortem Human Subjects with Recurrent Major Depression

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Background: Despite effective treatments, the molecular pathophysiology of depression is still being characterized. The cortical limbic circuit plays a major role in the pathophysiology of depression. Decreased GABAergic function has been suggested in the anterior cingulate cortex (ACC) in depression, while treatment of depression results in gene expression changes across brain circuits and molecular pathways. Two genes activated by antidepressant treatment include somatostatin (SST) and nerve growth factor inducible (VGF), although primary evidence for depression-related changes are lacking.

Methods: ACC mRNA from 51 age- and sex-matched pairs of recurrent depressed human post mortem subjects were analyzed for differential expression by microarray and quantitative PCR (qPCR).

Results: ACC mRNA of VGF and SST are significantly downregulated in MDD subjects to ~80% of control expression (p<0.05). After separation of subjects into male and female subgroups, there is a further difference in downregulation of both genes. In depressed females SST expression is ~60% (p<0.05) of control expression, while depressed males show ~87% of control expression. VGF expression in depressed males is ~65% (p<0.05) of control expression and females show ~80% of control expression.

Conclusions: Our results suggest a primary depression-related pathology affecting SST-bearing GABAergic interneurons in ACC. Moreover, the identification of decreases in two neuropeptides otherwise induced by antidepressants and BDNF suggest that the molecular underpinnings of the illness and its treatment are overlapping in ACC of depressed subjects.

Source of Funding: National Institute of Mental Health (MH077159).

Improvements to Cognitive and Visuo-Perceptual Task Performance in Dementia with Lewy Bodies with Galantamine

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Background: The McKeith et al1 consensus criteria for dementia with Lewy bodies (DLB) identified deficits to attention and visuospatial ability to be especially prominent central features of the condition. Galantamine is effective in the symptomatic treatment of Alzheimer’s disease (AD). In addition to acetylcholinesterase inhibition, galantamine acts as an allosteric modulator of neuronal nicotinic acetylcholine (ACh) receptors. Recent studies have suggested that this additional nicotinic action may underlie the early on-set benefits of galantamine to aspects of attention seen in AD patients,2 which have been shown to significantly exceed those of donepezil.3

Methods: This was a multicenter, investigator-initiated, open-label, flexible-dose (8–24 mg/day), 24-week study of galantamine in 50 patients with mild to moderately severe DLB. Mean age was 76.5 years (range 50–91). There were 29 male and 21 female patients, and the mean Mini Mental State Examination (MMSM) at baseline was 20.8 (range seven to 30). The Cognitive Drug Research (CDR) System4 was administered to assess specific aspects of cognition including major aspects of attention, working memory and episodic memory. In addition the CDR visuo-perceptual battery was administered to assess aspects of perception and the discrimination of various visual images.

Results: All aspects of cognitive function assessed with the CDR System improved with treatment; these reaching statistical significance for power of attention at 12 weeks and quality of episodic memory at 12 and 24 weeks. Small effect size (0.2–0.46) improvements were seen to other aspects of cognitive function and to performance on the visuo-perceptual battery.

Discussion: The improvements to power of attention and quality of episodic memory in DLB seen in this study have been seen previously with other anticholinesterases.1 The improvements to visuo-perceptual performance suggest that such assessments may be useful in future work. These findings support the recommendations of McKeith, et al.,1 that outcome measures in DLB trials should include specific measures of attention and visual perception. The recommendation for attention as an outcome measure was based on data from computerized tests, which also bring methodological advantages to clinical trials, including ease of administration, standardization of testing and facilitation of data collection and processing. The similarity of the attention deficits in DLB to those in Parkinson’s disease dementia (PDD) have been recognised,5 and rivastigmine was found to produce a marked improvement in the CDR power of attention in the pivotal registration trial for the compound in PDD.6 The nicotinic action of galantamine may therefore suggest that the various nicotinic receptor agonists under development could be useful in treating the attentional deficits in both DLB and PDD.

Source of Funding: Jansen-Cilag (protocol GAL-DLB-OL).

Literature References:
5. CDR System, www.unitedbiosource.com
Session II–51

Evaluating Functional Outcomes in Employed Outpatients with Major Depressive Disorder Treated with Desvenlafaxine 50 mg
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Background: This is the first study to assess the efficacy of desvenlafaxine (administered as desvenlafaxine succinate) for improving depressive symptoms and functioning exclusively in employed patients with major depressive disorder (MDD).

Methods: Gainfully employed (≥20 hours/week) male and female outpatients with MDD were randomly assigned (1:2 ratio) to receive 12 weeks of double-blind treatment with desvenlafaxine 50 mg/d or placebo. The primary and key secondary outcome measures were the Hamilton Rating Scale for Depression (HAM-D17) and Sheehan Disability Scale (SDS). Secondary outcome measures included Clinical Global Impressions (CGI), Montgomery-Asberg Depression Rating Scale (MADRS), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), HAMD-17 work and activities item, worry anxiety tension scale, stress and social support scale, and utilization and cost questionnaire. Analysis of covariance was used to compare differences in mean changes from baseline between the desvenlafaxine and placebo groups at Week 12 (last observation carried forward). Primary analyses were performed with data from the intent to treat (ITT) population. Analyses of data from a predefined modified ITT (mITT) population, defined as the ITT population with baseline HAMD-17≥20, provided supportive information. The occurrence of adverse events (AEs), discontinuations due to AEs, serious adverse events (SAEs), and Arizona Sexual Experience Scale (ASEX) scores were assessed.

Results: In the ITT population, mean baseline scores for the desvenlafaxine (n=285) and placebo (n=142) groups on the HAMD-17 were 22.0 and 21.8, and on the SDS were 19.8 and 20.4. The adjusted mean difference between desvenlafaxine and placebo at Week 12 was 2.1 (p=0.002) on the HAMD-17 and 1.3 (p=0.067) on the SDS. For the mITT population, baseline scores for desvenlafaxine (n=208) and placebo (n=102) on the HAMD-17 were 23.8 and 23.9, and on the SDS were 20.1 and 20.8; adjusted mean differences at Week 12 were 2.6 (p=0.002) on the HAMD-17 and 2.1 (p=0.017) on the SDS. Significant differences were observed on the following secondary measures (ITT population): CGI, MADRS, Q-LES-Q, and HAMD-17 Work and Activities subscale by assessment. The occurrence of AEs, SAEs and discontinuation due to AEs were comparable between groups and consistent with previous desvenlafaxine studies. There was no evidence of worsening in sexual functioning on the ASEX and the magnitude of change was comparable between desvenlafaxine and placebo.

Conclusions: These data demonstrate the efficacy of desvenlafaxine 50 mg/d for treating MDD in gainfully employed adults. There were no new safety or tolerability concerns. Although the difference between groups on the SDS fell short of the conventional threshold for statistical significance, the totality of data suggests improvements in functioning.

Source of Funding: Pfizer, Inc.

Session II–52

Rates of Metabolic Risk Factors in Major Depressive Disorder (MDD) with Psychotic Features: No Difference in Risk Compared to Those with MDD without Psychotic Features
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Background: Studies in schizophrenia have reported an association of metabolic risk factors, including elevated glucose, elevated triglycerides, decreased high-density lipoprotein (HDL), as well as hypertension, with schizophrenia, independent of treatment with antipsychotic medications. Although studies have also shown a strong association between metabolic risk factors unipolar depression, there is a paucity of research examining these risk factors in major depressive disorder (MDD) with psychotic features. This chart review is a first step in identifying the prevalence of metabolic risk factors in patients with MDD with psychotic features versus without psychotic features. We hypothesized that patients with the diagnosis of MDD with psychotic features would have higher rates of metabolic risk factors compared to patients diagnosed with MDD without psychotic features.

Methods: Charts were reviewed from patients on an inpatient psychiatric unit at a major northeastern hospital, with a diagnosis of MDD with or without psychotic features.

Results: There was no significant difference in age between patients with MDD with (M=49.59, SD=17.80) and without (M=51.15, SD=17.80) psychotic features. t(568)=0.45, p=0.65. Patients with MDD with psychotic features trended towards being more likely to be on an atypical antipsychotic, X²(1)=2.82, p=0.09. There was no difference in HDL between patients with MDD (M=45.15, SD=18.28) and MDD with psychotic features (M=44.75, SD=14.18), t(89)=0.09, p=0.93. No significant difference was found in triglyceride levels for patients with MDD (M=118.64, SD=65.63) and MDD with psychotic features (M=132.75, SD=77.54), t(88)=0.81, p=0.42. Patients with MDD with psychotic features were not more likely than patients with MDD without psychotic features to be taking medications for hypertension and/or have elevated blood pressure, X²(1)=0.63, p=0.43. Contrary to our hypothesis, patients with MDD without psychotic features were more likely than those with MDD with psychotic features to have diabetes, X²(1)=5.22, p=0.02.

Conclusions: To our surprise, patients with MDD with psychotic features did not manifest higher rates of elevated triglycerides, glucose, HTN or low HDL. A possible explanation for this finding is the unexpectedly high rates of atypical antipsychotic use in patients with MDD without psychotic features. Nonetheless, the findings underscore the importance of elucidating the mechanism by which psychiatric illness, antipsychotic medications and metabolic disarray are linked.

Source of Funding: Departmental Funds.

Literature References:
Session II–53

Impairment in Psychosocial Functioning Associated with Dysthymic Disorder in the National Epidemiologic Survey of Alcoholism and Related Conditions (NESARC) Study

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Background: Chronic depression is associated with impaired functioning. The National Epidemiologic Survey of Alcoholism and Related Conditions (NESARC) is a representative sample (N=43,093) of the U.S. non-institutionalized population aged 18 years and older. We hypothesized that individuals with chronic low-grade depression, dysthymic disorder (DD), would have more impaired functioning than individuals with acute major depression (MDD) or the general population (GP).

Methods: Diagnoses were generated by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (ADAUDIS-IV). Individuals with DD but without current MDD constituted the DD sample (N=328), while individuals with MDD of a duration <24 months, without lifetime dysthymic disorder, constituted the acute depression (AD) sample (N=712). All other respondents were classified as general population (GP) (N=42,052). Past year functioning was assessed by Supplemental Social Security Income (SSI), employment, and Medicaid statuses. Past month functioning was assessed by Short-form 12-Item Health Survey, version 2 (SF-12), with scores for social functioning, role emotional functioning and mental health, using odds ratios.

Results: Over the past year, compared to acute depression, persons with DD were less likely to work full-time (36.2% versus 44%; OR=0.70, CI=0.54, 0.92) and more often received SSI (13.9% versus 4.5%; OR=3.4, CI=2.0, 5.9) and Medicaid (20.2% versus 13%; OR=1.7, CI=1.1, 2.6). Compared to AD, dysthmics reported accomplishing less over the past month due to emotional problems and that emotional or physical problems interfered with social activities. Relative to the general population, respondents with DD were more likely to receive SSI (13.9% versus 2.9%; OR=4.6, CI 3.4, 6.2) and Medicaid (20.2% versus 5.9%; OR=2.9, CI 2.0, 4.1). Compared to GP, dysthmics reported accomplishing less due to emotional problems, and that emotional or physical problems interfered with both social activities and work functioning.

Conclusions: These findings confirm that significant psychosocial impairment is associated with DD in the community setting, making it a significant public health burden and highlight the importance of finding effective long-term treatments for this disorder.

Source of Funding: None.

Literature References:


Session II–54

Systematically Elicited Neuropsychiatric Adverse Events and Various Rating Scale Assessment of Withdrawal Symptoms in Smoking Cessation Trials

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Background: Smoking cessation, with or without treatment, is associated with nicotine withdrawal which includes a constellation of neuropsychiatric symptoms such as anxiety, sleep disturbance, depression, irritability, anger and restlessness that peak in the first week, can last for several weeks, and can be severe in some smokers.1 Limited information exists regarding the frequency, degree, time course and extent of neuropsychiatric symptoms. In order to better characterize nicotine withdrawal, possibly identify new symptoms of withdrawal and establish their utility in a clinical setting, a systematic neuropsychiatric adverse event (NPAE) questionnaire and a variety of clinician and self-report rating scales were administered to quitting smokers.

Methods: Fifty-five smokers average age 33.8 (73% male) who smoked an average of 16.8 years with a mean Fagerström of 7.3 and no psychiatric illness (via Structured Clinical Interview for DSM Disorders [SCID]) were examined when quitting on placebo as part of a double-blind study consisting of a two week titration period with continued smoking, a two week forced quit inpatient period, and an eight week outpatient abstinence period. NPAEs were solicited systematically through the use of the Systematic Assessment for Treatment Emergent Events (SAFTEE). Neuropsychiatric symptoms were measured via the Montgomery Åsberg Depression Scale (MADRS), the Hamilton Rating Scale for Anxiety (HAMA), the Overt Aggression Scale–modified (OAS-m), the Barratt Impulsiveness Scale (BIS) and the Social Dysfunction and Aggression Scale (SDAS).

Results: Fifty-two of 55 (94.5%) subjects reported at least one adverse event (AE) on the SAFTEE and one discontinued treatment due to an AE. Further, 23/55 (41.8%) reported a psychiatric adverse event during the trial with the majority of AEs associated with anxiety disorders and symptoms (14.5%), depressed mood disorders and disturbances (9%) and sleep disorders and disturbances (23%). Ratings scales showed a transient increase in symptomatology during the two week inpatient period that peaked at Week 3, but typically reverted to baseline levels one week following the inpatient period. The largest changes during the inpatient treatment period were seen on the HAMA (3.21±3.2) and the MADRS (1.90±2.7).

Further, when applying thresholds (≥14) based on predefined clinical criteria 15% and 5% of subjects crossed threshold on the HAMA and MADRS respectively.

Conclusions: Systematic NPAE reporting and various neuropsychiatric rating scales have clear utility in characterizing the type, extent and time course of nicotine withdrawal symptoms and may be especially helpful in dissociating the NPAE profiles of smoking cessation drugs from those typically associated with withdrawal.

Source of Funding: Pfizer, Inc.

Literature References:

**Session II–55**

**High-Dose Modified Release Escitalopram in Adults with Major Depressive Disorder: A Comparison with Low-Dose Immediate Release and Placebo**

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**Objective:** To compare the efficacy, safety, and tolerability of escitalopram modified release (MR) 28 mg/d, escitalopram immediate release (IR) 10 mg/d, and placebo in adults with major depressive disorder (MDD).

**Methods:** An eight-week double-blind, multicenter, randomized, placebo-controlled, parallel-group, fixed-dose study comparing escitalopram MR 28 mg/d, escitalopram IR 10 mg/d, and placebo. Eligible patients (18–65 years) had DSM-IV-TR–defined MDD, Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥26, Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score ≥15, and score ≥2 on Item 1 (depressed mood) of the 24-item Hamilton Rating Scale for Depression (HAM-D24). Primary efficacy parameter: MADRS total score change from baseline to Week 8 (last observation carried forward [LOCF]). The primary comparison was between escitalopram MR and placebo; if this difference was statistically significant at the 0.05 level, comparison between escitalopram MR and IR was then performed at the 0.05 level. Secondary/additional efficacy parameters included change from baseline to Week 8 on the 24-item HAMD, 17-item HAMD, QIDS-SR, and Clinical Global Impressions-Severity (CGI-S), and Week 8 CGI-Improvement score. Safety/tolerability assessments: adverse event (AE) reports, clinical and laboratory parameters and safety rating scales.

**Results:** Of 877 randomized patients (mean baseline MADRS total score=32.5), 25.4% discontinued prematurely (placebo, 24.1%; MR, 28.0%; IR, 23.7%); between-group differences were not significant. MADRS total score change from baseline to Week 8 was significantly greater for both escitalopram MR (LOCF; LSMD=–3.3; p<0.001) and IR (LOCF; LSMD=–2.9; p<0.001) relative to placebo. No significant differences were observed for escitalopram MR versus IR on MADRS change from baseline (LSMD=–0.4; p=0.660) or any additional efficacy parameter. Both escitalopram MR and IR achieved statistically significant differences versus placebo on all additional efficacy measures (p<0.05). Rates of discontinuation due to AEs were 3.2%, 7.1% and 5.0% for placebo, escitalopram MR, and escitalopram IR, respectively. Treatment-emergent AEs (TEAEs) for escitalopram MR and IR were slightly higher than placebo. The most common TEAEs in either escitalopram group (≥5% and greater than placebo) were headache, nausea, diarrhea, insomnia, dry mouth, somnolence, fatigue and nasopharyngitis. Mean changes in clinical laboratory parameters were small in magnitude in all treatment groups.

**Conclusions:** Escitalopram MR 28 mg/d and escitalopram IR 10 mg/d compared with placebo demonstrated significant improvement on all key efficacy parameters and both were well tolerated. No significant improvements were noted with escitalopram MR relative to escitalopram IR.

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

**Literature References:**

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**Session II–56**

**Adherence Rates for Antipsychotic Medications at Clinically Recommended Doses**

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**Background:** Partial adherence with mental health pharmacotherapy has been associated with an increased risk of clinical worsening, relapse, and rehospitalization. Additionally, there is accumulating evidence that sub-therapeutic dosing of second-generation antipsychotics (SGAs) is widespread in clinical practice, resulting in suboptimal disease control. However, further work is necessary to understand the clinical course of Medicaid patients who receive clinically recommended doses of SGAs. The objective of this study was to examine SGA medication adherence in patients prescribed aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone.

**Methods:** Medicaid claims data (2001–2008) from eight states were analyzed for patients with International Classification of Diseases (ICD) 9CM codes for schizophrenia (295.xx). The observation period was 18 months per unique patient (six months pre-index period, during which patients did not receive an SGA, followed by a 12-month post index utilization period) to determine if their medication possession ratio (MPR) was ≥80% (criterion for adherence).

**Results:** A total of 12,133 patients met inclusion criteria, with 59% (N=7,213) taking clinically recommended doses by day 61 of their follow-up period. For patients on recommended medication doses, 59% (N=4,274) were adherent with their SGA treatment (risperidone 65%, aripiprazole 63%, olanzapine 59%, quetiapine 59% and risperidone 57%). A logistic regression analysis including baseline covariates (age, gender, race, Charlson co-morbidity score and specific psychiatric co-morbidities) determined that patients on olanzapine (OR=0.74, 95% CI=0.60–0.91), quetiapine (OR=0.71, 95% CI=0.57–0.89) and risperidone (OR=0.70, 95% CI=0.57–0.85) were statistically significantly less adherent (p<0.005) than patients on ziprasidone. The odds ratio for aripiprazole was 0.83 (95% CI=0.68–1.06) compared to ziprasidone (p=0.144).

**Conclusions:** After their initial SGA start, less than two-thirds of Medicaid patients with schizophrenia were receiving clinically recommended doses by two months. In addition, less than two-thirds of patients on recommended doses were adherent (MPR ≥80%) with their therapy for one year after their SGA start date. Ziprasidone and aripiprazole had the highest rates of adherence of the five SGAs studied. Our results, in a sizeable Medicaid cohort, confirm the impression that patients with schizophrenia tend to receive suboptimal SGA treatment. In addition, the data suggest variation in patient adherence of specific SGAs, which may impact longer-term mental health outcomes and costs.

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

**Literature References:**
**Session II–57**

**Doctrate Level U.S. Positive and Negative Syndrome Scale (PANSS) Raters Score Higher on a Measure of Interview Quality than Non-Doctorate Level Raters**

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**Background:** We have previously reported substantial regional differences in the use of doctorate level raters in schizophrenia clinical trials with the lowest use in the U.S. compared to the rest of the world.1 The impact of educational level on the quality of the ratings interview in clinical trial settings is not well defined. We conducted a post-hoc- analysis to determine if the educational level of Positive and Negative Syndrome Scale (PANSS) raters in the U.S. was associated with the quality of the ratings interview.

**Methods:** We examined the relationship between the educational level (doctorate versus non-doctorate) of 100 U.S. PANSS raters and competency to conduct an interview as measured by the total score on the Research Interview Assessment Scale (RISA). All raters were undergoing training to rate in multi-center international schizophrenia clinical trials. The RISA is a 16-item scale that assesses four domains of interview quality, demonstrates high levels of inter-rater and intra-rater reliability and is highly correlated with other measures of interview competency.2

**Results:** The mean total RISA score of U.S. doctorate level raters (mean=27.8, n=45) was higher than non-doctorate raters (mean=26.2, n=55) (t=2.3, df=94, p<0.02). (unequal-variance t). The variance in the total RISA score of the non-doctorate raters was larger than that of the doctorate variance by a factor of 2.2 (p<0.001). The same pattern was found in a larger international sample (n=452), but the proportion of non-doctorate raters was much lower than in the U.S. sub-sample.

**Conclusions:** Interview quality is an important factor in the validity and consistency of clinical trials ratings. In this post-hoc analysis PANSS raters with doctorate degrees on the whole exhibited higher quality interview skills than non-doctorate raters. Moreover, among non-doctorate raters there was significantly more variance in the total RISA score (reflecting variation in interview quality) than among doctorate level raters. The current findings must be viewed in light of the possibility of sampling bias because all the raters were trained by United BioSource Corporation (UBC).

**Source of Funding:** United BioSource Corporation.

**Literature References:**


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**Session II–58**

**Do Recruitment Sources Impact Study Outcome: Assessment by Computer and Site-Based Raters**

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**Background:** Concerns about slow sample accession in clinical trials have prompted a variety of strategies that attempt to bolster recruitment. Recent large studies often extend local recruitment efforts by adding resources from experienced national recruitment vendors. Little data is available however, that compares outcomes for patients recruited from different sources (e.g., usual care providers versus mass media). Speculations about the high failure rates in central nervous system (CNS) studies include concern that subjects are not always representative of patients seeking treatment for the disorder under study. Computer administered assessments offer opportunities to collect data directly from subjects across global sites and provide a useful standard for exploring hypotheses regarding the performance of recruitment strategies. Analysis of data comparing ziprasidone to placebo on the site-based rater’s (SBR) and computer ratings found no significant differences between the treatment groups. This presentation provides the outcomes for subjects based on the referral source.

**Methods:** Computer administered assessments (Diagnostic Validation, MADRScomp) were included in a double-blind protocol that randomized 303 bipolar I subjects to adjunctive treatment with ziprasidone versus placebo for acute depression. The primary outcome variable was change from baseline to endpoint MADRSComp score. Computer diagnostic assessment interviews were scored (0–100) using the Bipolarity Index, a measure of diagnostic confidence. Quality ratings were defined based on the absolute value of the difference between the MADRScomp and MADRSstat baseline and categorized on a zero to four ordinal scale.

**Conclusions:** Subjects that entered the trial based on the recommendation of the psychiatrists’ office or another medical office had tandem SBR and computer assessment ratings that were more concordant than subjects responding to mass media. These subjects also had Bipolarity Index scores demonstrating greater confidence in a Bipolar I diagnosis. Computer assessments provide an opportunity to directly collect information from subjects that might facilitate design and testing of interventions to mitigate the potential for study failure.

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**Source of Funding:** The parent study was funded by Pfizer, Inc.; this poster is supported by Concordant Rater Systems.

**Literature References:**


Session II–59

Biomarker Screening for Alzheimer’s Disease: When to Screen and How Often

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Background: The initiation of treatments for the underlying pathology of Alzheimer’s disease (AD) would ideally be based on biomarker screening tools allowing identification of pre-symptomatic individuals, preventing future incident AD cases (IACs). Current evidence shows promise for screening measuring concentrations of AD markers in cerebrospinal fluid. Population-level screening initiatives require guidelines specifying when to screen and if/when to re-screen. A computer simulation evaluated the effect of screening/re-screening age on the rates of IACs.

Methods: A time-to-event stochastic model estimate the impact screening/treatment on cases of dementia of the Alzheimer’s type using current diagnostic criteria. Sensitivity/specificity of the test were set at 0.90, treating on positive screens. Hypothetical treatment slowed progression by 50%. Transition probabilities are derived from literature-based incidence of AD.1

Results: Age at first screening and frequency of screening were both varied. In a sample of 100,000 patients, AD-cases avoided were highest when screening 75 year olds every five years. The maximum cases avoided when initiating screening at age 55 occurred when screening every five years until all-cause death. For age 65, rescreening every 10 years avoided 3,596 AD cases compared to 4,848 cases screening every five years.

Conclusions: Although screening at earlier ages avoided substantial numbers of AD cases they represent a smaller percentage of those age 55 and 65. Screening at age 75 avoids similar numbers of cases in magnitude but a higher percentage of the population that age. Regardless of screening age, a screening test of the type described here has the potential to substantially reduce societal burden of AD given the availability of effective treatment.

Source of Funding: National Institute of Health (SBIR Grant 1R43MH082585-01A1), Eli Lilly and Company

LiteratureReferences:

Session II–60

Predictive Function of Treatment Outcomes in Patients with Schizophrenia

Douglas Vanderburg, M.D., M.P.H., Ofer Agid, M.D., Cynthia Siu, Ph.D., Elizabeth Pappadopulos, Ph.D., Shitij Kapur, M.D., Ph.D., F.R.C.P.C.

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Background: The objective of this study was to examine clinical predictors, early reduction in psychosis (within the first two weeks), and early tolerability/side effect measures (within the first six weeks) with antipsychotic treatment in schizophrenia. We integrated these early response measures into a long-term functioning prediction model and developed a scoring algorithm based on these early response indicators.

Methods: The analysis data-set was based on a double-blind, six-month continuation study of ziprasidone and olanzapine (N=94), which showed comparable efficacy between the treatment groups at all time points. A multivariate score function and a scoring algorithm for predicting likelihood of attaining >50% improvement in Global Assessment of Functioning (GAF) were developed from the regression coefficients of the Cox survival model. A risk estimate is then determined for each total score, using the risk ratio (relative to low risk state) instead of absolute risk. The performance and predictive accuracy of the scoring algorithm were based on c-statistics for discrimination (area under the receiver operating characteristics curve [AUROC] and Hosmer-Lemeshow statistics for calibration (observed and predicted event rates).

Results: At Week 2, the majority of ziprasidone (75%) and olanzapine (70%) patients showed greater than 25% improvement in Brief Psychiatric Rating Scale (BPRS) psychotic symptom subs-scale score. At up to six months of follow-up, 52 (55%) subjects met the responder criterion of >50% improvement in global functioning. Early psychotic symptom responders (Week 2) showed significantly more improvement in global functioning than early nonresponders at all time points (Week 6 and Month 6) (all p<0.05), confirming early response within the first two weeks of antipsychotic treatment as an indicator of continued responsiveness to treatment over at least six months. A multivariate score function based on baseline scores, early reduction of psychotic symptoms at two weeks (p<0.05), and percentage of weight change observed at six weeks (p<0.05), showed statistically acceptable predictive performance based on c-statistics (AUROC=0.83; 1-specificity versus sensitivity curve).

Conclusions: Our findings suggested that very early improvement in psychotic symptoms predicts long term global functioning. A scoring algorithm incorporating a psychotic symptom sub-scale score and side-effect measures can be developed for predicting patients’ likelihood of achieving favorable, long-term treatment outcomes.

Source of Funding: Pfizer, Inc.

LiteratureReferences:
Efficacy of Iloperidone in Schizophrenia: Analysis of a Six-Week Placebo- and Active-Controlled Randomized Trial in Patients Completing 14 Days Treatment

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Background: Iloperidone is a mixed D2/5HT2 antagonist atypical antipsychotic recently approved for the treatment of schizophrenia. Several studies have described its efficacy and safety in schizophrenia and schizoaffective disorder.1,2 A published multicenter trial (study ILO522 3005) comparing iloperidone to placebo and risperidone in patients was deemed a pivotal study based on analysis of patients with schizophrenia. As differential dropout rates at the start of the trial occurred possibly related to titration requirements, we analyzed the trial in patients receiving >14 days treatment, the time required for steady state to occur with iloperidone.

Methods: Patients aged 18–65 years with an acute exacerbation of schizophrenia according to DSM-IV criteria and a Positive and Negative Syndrome Scale (PANSS) Total (PANSS-T) ≥60 at baseline were included in this post-hoc analysis; patients with schizoaffective disorder were excluded. Patients were randomized to receive twice daily iloperidone (12–16 mg/d; 20–24 mg/d), risperidone 6–8 mg/d, or placebo. Efficacy outcomes were: the Brief Psychiatric Rating Scale (BPRS), the PANSS-T, and the PANSS positive and negative (PANSS) subscale. An analysis of covariance on the intent-to-treat population who received treatment >14 days was conducted (last observation carried forward [LOCF] n=420).

Results: For all three active-treatment arms, similar and statistically significant mean adjusted reductions from baseline (BPRS) compared to placebo were identified (p<0.01): 11.2 (iloperidone 12–16 mg/d), 11.7 (iloperidone 20–24 mg/d), and 12.1 (risperidone). Most other efficacy variables showed significant improvement with both iloperidone doses versus placebo. Differences between iloperidone and risperidone were not statistically significant.

Conclusions: In patients who do not drop out during the titration period (while steady-state concentration is being achieved), iloperidone significantly improves symptoms associated with schizophrenia and is comparable to risperidone. Iloperidone is a new treatment option for patients with schizophrenia.

Source of Funding: Novartis Pharmaceuticals Corporation.

Literature References:

Absolute Risk versus Risk Ratio in Framingham Scoring Algorithm for Prevention of Cardiovascular Risk in Psychiatric Disorders

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Background: Previous studies applying Framingham Risk Score (FRS) have been all focused on “absolute risk,” i.e., the probability of developing CHD over a given period of time.3 This might not be most appropriate for the individuals in schizophrenia population, since the original Framingham Cox Survival model was developed based on a white middle-class population from the Framingham Heart Study (FHS).

Methods: The objective of this paper was to investigate whether risk ratio (relative to low risk state) can provide more accurate risk estimate than the usual absolute risk score. We calculated estimates for low risk based on optimal blood pressure (systolic<120 mm Hg and diastolic<80 mm Hg), total cholesterol (TC) 160 to 199 mg/dL, HDL-C of 55 mg/dL in women, no diabetes and no smoking.4 To recalculate the FRS risk estimates, we need to replace (a) the baseline risk (RISK0) in FRS function, and (b) the mean risk factors GMEAN (e.g., mean age, percentage of smoker or other risk categories) with values from the schizophrenia populations.

Results: The average FRS risk categories in Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) and FHS studies were different in age (40 in CATIE versus 49 in FHS), total cholesterol ≥240 mg/dL (20% versus 26%), HDL<35 mg/dL (25% versus 11%), Diabetes mellitus (women 16% and men 11%) versus (women 4% and men 5%), and smoker (women 56% versus men 73%) in CATIE versus (women 38% and men 40%) in FHS. Specifically, for age 55–59 women, the FRS 10-year absolute risk was 13.3% in both the CATIE study and the schizophrenia study,12% in FHS,1 and 7% low risk using FHS RISK0=3.75%.5 Replacing this FHS RISK (3.75%) with the baseline risk (6.3%) from CATIE study yielded a different absolute FRS risk (21.4%) for the schizophrenia population in FHS6 and a new low risk value (11.3%). However, the risk ratio (10-year absolute risk / low risk) was 1.9 independent of what baseline risk value was used: 13.3%/7% for FHS RISK0 and 21.4%/11.3% for CATIE RISK0. We developed a simple proof to show that risk ratio (relative to the low risk state) does not depend on baseline risk (RISK0) and mean risk factors GMEAN when the cumulative hazard is small, and hence is more useful to be compared across populations.

Conclusions: Our findings suggest that risk ratio (relative to low risk state) instead of absolute risk might be more appropriate for prediction of cardiovascular risk in schizophrenia patients using Framingham Scoring Function before baseline risk can be established.

Source of Funding: DataPower, Inc.

Literature References:
Session II–63

GABA, Neuronal Synchrony and Neurocognitive Efficiency in Schizophrenia

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*In an earlier phase of investigator’s career, the abstract presents a proposed research design.

Background and Proposed Research Design: Cognitive deficits in schizophrenia are inadequately treated. Uncovering their etiology would inform the development of specific treatments for this disabling aspect of the illness. We propose to test a new model that posits a causal relationship among impaired working memory, disordered neuronal synchrony and prefrontal GABA levels in schizophrenia. According to this model, disruption of gamma band neuronal synchrony, possibly secondary to impairment of dorsolateral prefrontal cortex (DLPFC) GABAergic neurons, contributes to cognitive deficits in patients with schizophrenia. Schizophrenia patients have been shown to have deficits in GABAergic populations in the DLPFC on neuropathology, but the relationship between GABA function and neuronal synchrony cannot be studied postmortem. With the support of Columbia’s Clinical Translational Science Award (CTSA) (Chen, PI; Kegeles, Co-PI), we will collect magnetic resonance spectroscopy (MRS) measures of GABA. This novel combination of in vivo MRS measures of GABA with high-density electroencephalogram (EEG) measures indexing neuronal synchrony during a working memory task offers the potential to further our understanding of the pathophysiology of schizophrenia and to identify novel therapeutic targets for remedying cognitive deficits.

Methods: Our independent variable is diagnosis and dependent variables are MRS measures of GABA, electroencephalogram (EEG) measures, and working memory performance. Routine measurements of GABA levels in the left DLPFC and anterior cingulated cortex will be made on a 3.0 T GE MR system, using the standard volume-selective PRESS J-editing difference method with a commercial eight-channel phased-array head coil. Sixty-four-lead EEG will be recorded during the performance of a working memory task. Power and phase synchrony of gamma frequency band of EEG will be investigated. Working memory performance will be determined by reaction time and accuracy.

Preliminary Results: There was a significant relationship between GABA measures of left DLPFC and power of gamma frequency band (30–56 Hz) of F3 electrode (two-tailed Pearson’s correlation coefficient, n=11, r=0.652, p=0.030). We also found that patients had a trend of lower power in the gamma frequency band than controls (independent-samples t-test, t=2.263, df=8.277, p=0.052).

Discussions: The proposed design is feasible with promising results and asks key questions about the pathophysiology of core deficits in schizophrenia. It will help identifying novel treatment targets that can have a major impact on public health.

Source of Funding: Lieber Center, Columbia University Clinical Translational Award.

Literature References:

Session II–64

Feasibility Trial for Information Technology Enabled Treatment of Adolescent Depression

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Background: The need for treatment of adolescent depression arises from the observation that a large number of adolescents (between 20-30%) are untreated and 20% of untreated adolescent depression have an individual development and society as a whole. Cumulative prevalence rates of MDD among adolescents are reported to be 12–22% by the age of 21 years. Effective treatments have been developed for adolescent MDD. Unfortunately, multiple barriers interfere with the implementation of “gold standard” care particularly due to the scarcity of trained child psychiatrists and other mental health clinicians. This trial focuses on testing of an Information Technology Enabled Management System for Treatment of Adolescent Depression (ITEMS-TAD) that guides nurses in the delivery of evidence-based treatment for adolescent MDD.

Methods: We developed a prototype of ITEMS-TAD that includes four main components: a computer assisted telephone interview, a multi-source integrated treatment database, a set of treatment adjuster algorithms, and a multimedia training program. We conducted a Rapid Iterative Testing and Evaluation Study (RITE) with eight nurses and adolescents to refine the content and assess the usability of the technology in its delivery; then a pilot efficacy study (PES) with four nurses and 30 adolescents to evaluate preliminary indicators of efficacy of the ITEMS-TAD approach, monitor therapeutic alliances, and assess patient and provider satisfaction and acceptance. Both the RITE and the PES consisted of three phone-based CBT sessions focusing on teaching basic cognitive behavioral skills to study adolescents. Sessions were delivered weekly and lasted approximately an hour.

Results: To date, eight subjects have completed the RITE and 11 the PES. Preliminary analyses suggest that nurses adhered to the principles of therapeutic alliance. Eight of the adolescents reported high levels of satisfaction. Two of them expressed some concerns with the length and materials used. So far, nearly all subjects (10) found the project useful and would consider a regular course of treatment.

Conclusions: We aim to demonstrate the ability nurses to establish a positive working relationship with adolescents and families and to teach basic cognitive behavioral skills. If successful, the approach used in this trial will be refined, expanded, and scaled-up to develop a fully explicated version of ITEMS-TAD in Phase II.

Source of Funding: National Institute of Mental Health (R01MH08350A).

Literature References:

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A Comparison of Statistical Approaches Used to Evaluate Change in Cognitive Function Following Pharmacologic Challenge: An Example with Lorazepam

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1CogState Ltd., Melbourne, Victoria, Australia, 2Yale University School of Medicine, New Haven, CT, 3Rhode Island Hospital, Warren Alpert Medical School, Brown University, Providence

Background: Cognitive tests are used commonly in psychopharmacological research to help understand the nature and the magnitude of the effects of licensed and novel compounds on cognitive function. While the science of cognitive change assessment has made considerable advances in recent years, the statistical techniques used to guide inferences about differences between drug and placebo conditions have not been considered in the same detail, especially in light of recent advances in modeling repeated data.

Methods: Data from a randomized, placebo-controlled, crossover study of the effect of an acute dose of lorazepam on cognitive function in healthy adults were analyzed using five statistical approaches (paired sample t-test, area under curve, repeated measures ANOVA, change from baseline, and linear mixed models).

Results: Linear mixed model approaches were superior to other statistical approaches with respect to results of significance testing and in magnitudes of estimated effect size change following lorazepam challenge.

Conclusions: Results of this study suggest that employment of linear mixed models, which permit examination of specific fixed effects (e.g., time, treatment, treatment x time) and that are not confounded by between-subject variability provide a sensitive approach to detecting the cognitive effects of pharmacologic challenges.

Source of Funding: National Health and Medical Research Council.

Literature References:

Efficacy of Valproic Acid, Lithium Carbonate and Carbamazepine in Maintenance Phase of Bipolar Disorder—A Naturalistic Study

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Maimonides Medical Center, Brooklyn, NY

Background: Bipolar disorder is a lifelong illness for 90% of patients who experience a manic episode. Maintenance treatment is usually recommended. Our goal was to look at the efficacy of lithium, depakote and tegretol as maintenance treatment of bipolar disorder in a naturalistic setting.

Methods: Two hundred-twenty-five outpatients with bipolar disorder were followed for up to 124 months, or until they had a manic or depressive episode, or dropped out of the study well 98 patients (43.6%) were taking lithium, 77 (34.2%) depakote, and 50 (22.2%) tegretol.

Results: A total of 103 patients (45.8%) had either a manic or depressive episode during the study period. Across the medication groups, 36.7% of the patients taking lithium (N=36), 54.5% of the patients taking depakote (N=42), and 50% of the patients taking tegretol (N=25) had either a manic or depressive episode at some point during the 124 month study period. The median survival time was 45.76 months for the entire sample, 36 months the depakote group, 42 months tegretol and 81 months for lithium. Fifty-two patients dropped out of the study well and 70 remained in the study well. A cox regression model evaluating the probability of having a manic or depressive episode among the three medications after controlling for several covariates showed that patients taking depakote had a significantly higher risk of having a manic or depressive episode than patients taking lithium. For patients taking depakote the hazard of having a manic or depressive episode was 1.63 (CI 1.01–2.63) times higher versus patients taking lithium. Thus, the hazard of becoming unstable was 38.5% lower in patients taking lithium compared to those taking depakote. There was a non-significant trend for greater maintenance efficacy of lithium versus tegretol and tegretol versus depakote.

Conclusions: Lithium patients had statistically better maintenance than the depakote group and a trend toward better maintenance versus the tegretol group in this naturalistic setting.

Source of Funding: None.

Literature References:
Bipolar disorder (BD), previously known as manic depressive illness, is a lifelong highly recurrent mood disorder characterized by periods of mania (bipolar I) or hypomania (bipolar II) that alternate with episodes of major depression (DSM-IV-TR). Several converging lines of biological evidence suggest possible mitochondrial dysfunction in BD. The current study focuses on the 16.6-kb mitochondrial genome (mtDNA); it seeks to (a) select a set of haplotype tagging single-nucleotide polymorphisms (hSNPs) that efficiently capture all common mtDNA variation in Europeans; (b) test those hSNPs for association with BD in two independent large-scale samples of European decent—a large-scale population-based sample and a family-based sample. Thus, the unprecedented sample size and wealth of phenotypic detail will be combined with recent advances in understanding the linkage disequilibrium (LD) pattern of the mitochondrial genome to perform a comprehensive genetic test of the hypothesis that mitochondrial DNA (mtDNA) variants influence BD susceptibility. This work may elucidate the potential role of common mtDNA variations in BD susceptibility and eventually lead to novel drug development that ameliorates human suffering.

**Source of Funding:** NARSAD Young Investigator Award.

**Literature References:**


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**Session II–68**

**Patients with Late-Life Depression Have Impairment on Neurocognitive Tests Sensitive and Specific for Dementia**

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North Carolina Neuropsychiatry Attention and Memory Centers, Raleigh

**Background:** Depression in late life may be associated with a greater risk of developing dementia. Late-life depression may involve, as part of the syndrome, cognitive impairment. If indeed cognitive impairment is inherent to both, then neurocognitive testing may be able to discover a similar pattern of impairment in both depression and dementia.

**Methods:** In this study, we did a cross-sectional analysis of subjects age 60 and above who had been diagnosed with either major depression (n=113) or dementia (n=68) or were normal controls (n=521), and who also did an extensive computerized neurocognitive battery (CNS Vital Signs).

**Results:** We found that poor performance on verbal memory, visual memory, the Continuous Performance Test, and the Perception of Emotions Test were best able to separate dementia patients from age-matched controls (Cohen’s d=2.2), and that patients with depression also did significantly worse on these tests compared to the controls (p<0.001), but not as badly as dementia patients (p<0.001).

**Conclusions:** We conclude that, consistent with the hypothesis that late-life depression includes cognitive impairment, patients with depression have a similar cognitive profile to those with dementia, but with a lesser degree of impairment. The results of this study are consistent with late-life depression as a risk factor for or prodrome of dementia.

**Source of Funding:** North Carolina Neuropsychiatry Attention and Memory Centers.

**Literature References:**

Session II–69

Genetic Findings of the Vasopressin/Oxytocin System and Childhood Aggression

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Centre for Addiction and Mental Health, Toronto, Ontario, Canada

Background: Childhood onset aggression is a complex behaviour with diverse theories about its etiology and little agreement on how to define the phenotype. There has been a growing recognition that heritable genetic factors may increase the susceptibility to aggressive behaviour and need to be included in explanatory models of how aggressive behaviour develops. For example, twin studies have shown that the callous-unemotional trait, as a subtype of aggression, has a high heritability, making it a good candidate for molecular genetic studies. While neurotransmitter systems have been implicated in the development and expression of aggression, recent studies in both animals and humans have demonstrated that the vasopressin/oxytocin system is strongly linked to aggressive behaviour; however, there are no genetic linkage or association studies exploring the association.

Methods: This sample has been described previously and consisted of 165 children, with a mean age of 11 years. Children were recruited via psychiatric referral and had at least a two-year history of aggressive behaviour. Inclusion criteria consisted of scores above the 90th percentile on the aggressive subscale of the Child Behaviour Checklist (CBC) and Teacher’s Report Form (TRF). The Callous-Unemotional subscale of the Antisocial Process Screening Device (APSD) was used to assess levels of the callous-unemotional trait. One single nucleotide polymorphism (SNP) in the AVPR1b gene and eight SNPs in the AVP/OXT gene region were genotyped in these children. Analyses compared genotype frequencies of the aggressive children with healthy comparison adult subjects. Analyses also compared scores on the callous-unemotional subscale of the APSD with genotype frequencies in the aggressive children.

Results: In the AVPR1b receptor, one SNP was significantly associated with aggression in the analysis of cases versus controls. In the AVP/OXT genes, three SNPs were significantly associated with the children’s scores on the APSD, indicating an association with the callous-unemotional trait.

Conclusions: The OXT/AVP gene system is associated with aggressive behaviour and with the callous-unemotional trait. This is the first study to demonstrate an association between the vasopressin/oxytocin gene system and childhood aggression. These findings identify potential new targets for the development of therapeutic pharmaceuticals.

Source of Funding: Centre for Addiction and Mental Health Foundation.

Literature References:

Session II–70

Neuropsychological Functioning in Patients with Bipolar Disorder with and without a History of Substance Use Disorders

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Massachusetts General Hospital, Harvard Medical School, Boston

Objective: Bipolar disorder is highly comorbid with substance use disorders. It is not known whether differences in cognitive functioning may explain why some people with bipolar disorder develop substance use disorders (SUD) and others do not. We hypothesized that abstinent bipolar subjects with a past history of substance use disorder would have problems with executive functioning and verbal memory compared to those with no history of substance use disorder.

Methods: Twenty-three subjects with bipolar I or II disorder and a past history of substance use disorder by DSM-IV criteria who were currently abstinent were compared to 33 subjects with bipolar I or II disorder with no substance use history. Neuropsychological tests including the Wechsler Test of Adult Reading (WTAR), Stroop and the Cambridge Neuropsychological Test Automated Battery (CANTAB), and mood ratings were performed. Differences between groups were analyzed using univariate and multivariate regression techniques. Results were adjusted for multiple comparisons where appropriate.

Results: No differences between groups were found on any of the neuropsychological tests. The results did not appear confounded by baseline clinical or demographic variables.

Conclusions: Differences in executive functioning, verbal or spatial memory, and intelligence do not appear to be associated with whether or not subjects with bipolar disorder have a history of substance use disorders, suggesting that neurocognitive traits do not explain drug and alcohol problems in these patients. If cognitive difference exist during periods of drug and alcohol, they do not appear to be persistent during prolonged abstinence.

Source of Funding: NARSAD Young Investigator Award.

Literature References:
Session II–71
Inhibitor-Induced, Dopamine Transporter-Mediated Oxidative Stress in Neuro2A Neurons
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Baylor College of Medicine, Baytown, TX

Background: Previous post mortem experiments in human cocaine users discovered increased striatal dopamine transporter (DAT) surface binding, which was inversely correlated with a total number of midbrain dopamine neurons.1 A net increase of 30–40% in axonal DAT surface levels can be accomplished in the face of a 17% overall loss of dopamine cells, because about three-fourths of terminal DAT is normally in reserve. In addition, acute inflammatory infiltration was detected, indicating the decrease in cells was likely an acute effect. The same subjects also displayed reduced dopamine levels and reduced VMAT2 binding and immunoreactivity.2 Naturalistic, whole animal and experiments in engineered cells all indicate that increased DAT activity, increased dopamine flux and decreased VMAT2-mediated vesicular storage cause dopaminergic toxicity, possibly secondary to oxidative stress. We previously demonstrated that hDAT-expressing Neuro2A mouse neuroblastoma cells display increased dopamine transporter surface location and dopamine uptake after sustained cocaine exposure,3 which does not occur after other DAT inhibitors such as emphyllennidate, GBR12909, and d-amphetamine. In the present experiments, we compared the isolated and combined effects of various DAT inhibitors, external and internal dopamine and cocaine-induced increased DAT surface levels, on cell viability and indicators of oxidative and nitrosative stress. A better understanding of the role of DAT regulation and oxidative stress generation is necessary to fully predict the effects of DAT Inhibitors on dopamine neuronal function, in their role as long term treatments for stimulant dependence and attention deficit disorder.

Methods: As previously described, hDAT- and non-transfected N2A cells were grown using DMEM and FEBS. Some cells were treated with varying concentrations of dopamine, 10–5 to 10–7 M for varying time intervals. Inhibitor effects (10–6 M) were also examined both alone, and after alternating treatments with dopamine. Some hDAT-N2A cells were exposed to cocaine or other inhibitors for a 24-hour period, then washed and cocaine replaced by dopamine, 10–6M, for 12 hour periods, for several cycles, over four or six days. In this way, cells were exposed to inhibitor-induced altered levels of surface DAT followed by exposure to dopamine. Cell viability was detected using the cell viability kit (Invitrogen, Inc.). Oxidative stress markers were detected using TBARS (OxiTek Kit, Zeptometrix, Inc.), and nitrative reactive species (RNS) using the GRESS reagent (Invitrogen, Inc.).

Results: The results demonstrated limited effects of cocaine and other inhibitors on cell number in either cell type, a dose-related effect of dopamine on both cells, which was greater in hDAT-expressing cells; and an even greater effect in hDAT-expressing cells treated with alternating dose of cocaine and dopamine, compared to dopamine alone. Increases in both RNS and ROS were found after dopamine treatments, tending to be higher with increased presumed levels of intracellular dopamine. Further results and analysis will be presented.

Source of Funding: National Institute on Drug Abuse (15509 R01).

Literature References:

Session II–72
Effect of B-Adrenergic Blocker Propranolol on Physiological Responses to Smoking Cues Using Script-Driven Imagery in Healthy Smokers
Gladys Pachas, M.D.1, Sara Carlini, B.A.1, Roger Pitman, M.D.2, Scott Orr, Ph.D.3, A. Eden Evins, M.D., M.P.H.4

1Massachusetts General Hospital, Boston, 2Massachusetts General Hospital, Charlestown, 3Veterans Affairs Medical Center, Manchester, NH

Purpose: Each year over 430,000 people in the U.S. die from smoking-related illnesses. First line pharmacotherapies for smoking cessation double the smoking cessation rate over placebo. However, only 30–60% of people quit on a given smoking cessation attempt with effective pharmacotherapy and up to 90% of those who quit relapse within the first year. One process thought to be implicated in relapse is excessively powerful and persistent smoking-related memories that are easily activated by smoking-related cues, leading to drug craving, even after long periods of abstinence. Animal studies show that administration of propranolol after eliciting a memory (post-retrieval) will result in less physiologic reactivity to smoking cues one week later.

Materials and Methods: We conducted a randomized, double-blind placebo-controlled trial of a single dose of the B-adrenergic blocker, propranolol, followed by smoking memory reactivation with script driven imagery in treatment-seeking nicotine dependent participants. One week later, memories of the intense smoking experience are activated (script driven imagery) to evoke craving and to assess physiologic activation to smoking-related scripts. Primary outcomes were physiological responses measures: skin conductance (SC), heart rate (HR) and left corrugator electromyogram (EMG) and subjective rating of craving visual analogue scale (VAS).

Results: Fifty-four participants completed the study. There was a main effect of script type: smoking scripts increased physiological reactivity compared to neutral scripts for all measures (SC response M=0.04 SD=0.55 versus M=0.15 SD=0.19 p=0.018; HR response M=1.01 SD=1.27 versus M=0.88 SD=1.61 p=0.014; EMG response M=0.75 SD=1.63 versus M=0.60 SD=1.18 p=0.019; craving VAS M=4.65 SD=1.88 versus M=3.02 SD=1.95 p<0.001, respectively). Although there is no script type by medication interaction on any measure, this Treatment x Stimulus interaction effect suggested a trend towards smaller EMG responses to the smoking scripts one week after a single dose of propranolol, compared to the group receiving placebo (Propranolol M=0.48 SD=1.31 versus Placebo M=0.98 SD=1.86; p=0.082).

Conclusions: Exposure to smoking-related stimuli (personalized smoking scripts through script driven imagery procedure) had a significant impact on physiological responses to smoking cues and self-report of smoking urges compared to standardized neutral scripts in non-deprived, nicotine dependent smokers. Memory reconsolidation blockade with single dose propranolol following memory reactivation did not reduce physiologic response to smoking cues or subjective experience of craving one week later although there was a trend for a treatment by stimulus interaction in corrugator activation.

Source of Funding: National Institute on Drug Abuse (R21 DA025186).

Literature References:
### Session II–73

**Comparative Efficacy of Daily versus Split Dosing of Atomoxetine on School and Home Functioning in Children with Attention Deficit Hyperactivity Disorder (ADHD)**

Ope Akinnusi, M.D., Daniel A. Waschbusch, Ph.D., James G. Waxmonsky, M.D.

University at Buffalo, NY

**Rationale:** Comparative studies of once versus twice daily dosing of atomoxetine have demonstrated the efficacy of both strategies for treating attention deficit hyperactive disorder (ADHD) in adults without evidence of differential effects by dosing pattern. However, all prior work relied on subjective symptom reports, and no such study has been completed in children.

**Objective:** To compare the effect of single versus split dosing of atomoxetine on school and home functioning of children with ADHD.

**Methods:** Post-hoc analysis compared efficacy of QAM versus BID Atomoxetine dosing during an eight-week randomized open label trial designed to compare the efficacy of behavior therapy (BT) alone versus BT plus atomoxetine. All subjects were started on QAM dosing. Switching to BID dosing occurred by Week 4 at the physicians’ discretion to address tolerability and efficacy concerns. Thirty-four subjects were maintained on QAM dosing while 22 went to BID dosing. There were no significant differences in demographics, baseline symptom severity or rates of BT usage between dosing groups. The mean dose was higher in the BID group (1.56 mg/kg/day versus 1.35 mg/kg/day, p<0.05). The primary efficacy measure was change in classroom rule violations scored by direct observation. Teachers and parents also completed ratings of disruptive symptoms, academic functioning and side effects.

**Results:** While both groups improved over time, there was a significantly greater decrease in classroom rule violations with QAM versus BID dosing (F=4.25, p<0.05, effect size (ES) =0.71). Teacher-rated oppositional defiant disorder symptoms (F=4.19, p<0.05, ES=0.65), peer relationships (F=5.17, p<0.05; ES=0.33), parent-child relationships (F=5.46; p<0.05; ES =0.50), percentage of daily classroom goals achieved (F=2.55, p<0.10; ES=0.28) and parent-rated academic functioning (F=4.06, p<0.05, ES=0.36) also favored the QAM group. There were no appreciable group differences in side effects.

**Conclusions:** Compared to split dosing, once daily atomoxetine dosing is associated with greater improvements in school and home functioning in children with ADHD with no worsening of tolerability. Results are limited by the secondary nature of the analyses and small N but merit further investigation.

**Source of Funding:** Eli Lilly, U.S.A.

**Literature References:**


### Session II–74

**Comparison of Cognitive Function in Patients with Treatment Resistant Depression, First Episode Depression and Healthy Control**

Jun Chen, M.D., Ph.D.; Yiru Fang, M.D., Ph.D.; Keming Gao, M.D., Ph.D.; Joseph R. Calabrese, M.D.

1Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, People’s Republic of China; 2Mood Disorders Program, Case Western Reserve University School of Medicine, Cleveland, Ohio

**Objective:** To compare the cognitive function of patients with treatment resistant major depression (TRD), first episode major depression (FED) and healthy control.

**Methods:** The cognitive functions of 53 patients with TRD and 21 with FED, and 20 healthy controls were accessed with neuropsychological tests including Wechsler Adult Intelligence Schedule (WAIS), Wechsler memory scale (WMS), Wisconsin Card Sorting Test (WCST) and Number Cancellation Test (NCT). The scores and subscale scores of these tests were compared between the groups by using two-tailed t-test, Wilcoxon rank test, covariance analysis with age and education and Chi-square test.

**Results:** Patients with TRD or FED had a lower Performance IQ (PIQ) score of WAIS compared with healthy control (p<0.01). Patients with TRD showed a much lower PIQ score than FED (p<0.05), especially in object assembly (OA) part of PIQ. Similarly, compared with the healthy control (p<0.01), patients with TRD or FED had significantly lower score of WMS memory quotient (MQ), long and short term memory, WCST number of categories completed (CC), response administered (RA) and percent conceptual level responses (PCLR) of WCST, correct number and score of NCT. On the other hand, patients with TRD or FED had significantly higher scores than the healthy control in WCST total time, error response time, perseverative errors (IPR) and percent perseverative errors (PPR) of WCST. Furthermore, the differences between patients with TRD and the healthy control in WCST error response time, PR, PPR, PCLR, correct number and score of NCT were greater than the difference in these variables between patients with FED and the healthy control.

**Conclusions:** Compared to healthy control, cognitive function impairments were observed in patients with TRD and those with FED although the later showed a lesser degree. The change of these cognitive impairments after successful treatment is worthy of further exploration.

**Source of Funding:** National Key Technologies Research and Development Program (2004BA720A21-02); National High-Tech Research and Development Program (2006AA02Z4430); Science and Technology Commission of Shanghai Municipality (064119533); Shanghai Jiaotong University School of Medicine, Natural Science Foundation (09XJ21024).

**Literature References:**


Session II–75

Improving Tic-Related Response Inhibition: Comparing the Effects of Dexmethylphenidate to No Medication in Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and Chronic Tic Disorders


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Objective: This is a pilot study using a Tic Suppression Paradigm (TSP) to test whether dexmethylphenidate (dMPH) can facilitate tic suppression in children and adolescents with attention deficit hyperactivity disorder (ADHD) and Tourette’s disorder (TD) or chronic tic disorder. The primary hypothesis is that dMPH will improve reinforced tic suppression.

Methods: Children with TD and ADHD were given dMPH on one day and no medication on another in randomized order. On both days, following a baseline period, subjects were reinforced for suppressing tics using a standard TSP.

Results: Data were analyzed on ten subjects completed to date. Relative to the no medication condition, tics were reduced when children were on dMPH. Reinforcing tic suppression produced lower rates of tics compared to baseline, but dMPH did not improve this ability.

Conclusions: Preliminary results of this study indicate replication of prior studies of behavioral tic suppression in youth with TD without ADHD; in addition, our results indicated tic reduction (and not tic exacerbation) with acute dMPH challenge in children and adolescents with ADHD and TD or chronic tic disorder.


Literature References:

Session II–76

Anatomical Evidence for Reticular Activating System and Cerebellar Involvement in Adults with Attention Deficit Hyperactivity Disorder: A Retrospective Analysis

Tony Ortiz, Ph.D.
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Background: There is a growing need to integrate data from functional brain imaging and neuropsychological assessment to elucidate the role of executive functioning in adults with attention deficit hyperactivity disorder (ADHD). 1 The current study examined functional differences (as measured by regional cerebral blood flow (rCBF)) between adults with ADHD and normal controls during a rest and concentration (CPT-I administration) scan.

Methods: Participants included 82 individuals that were recruited from a clinic in Southern California that provides neurological services including brain imaging. After screening for inclusion/exclusion criteria, there were a total of 41 participants per group. Single Photon Emission Computerized Tomography (SPECT) was used to examine Cerebral Blood Flow (rCBF). Rest and concentration brain images were processed using the Odyssey software and normalized to a standard anatomical space using Statistical Parametric Mapping Version 2 software (SPM) with gender as a covariate.

Results: Results from voxel-wise comparisons using Family-Wise Error (FWE) corrections demonstrated low rCBF in the left corpus callosum, t(72)=5.95, p<0.001, left pons t(72)=6.11, p<0.001, left medulla, t(72)=5.21, p<0.02, right superior frontal gyrus, t(72)=5.52, p<0.01 and right medulla t(72)=6.38, p<0.001 in the ADHD group when compared to the normal controls during the rest scan. During the concentration scan, low rCBF in the left corpus callosum, t(80)=7.17, p<0.001, left uncus, t(80)=5.55, p<0.004, left cerebellar tonsil, t(80)=6.04, p<0.001, right superior frontal gyrus, t(80)=5.33, p<0.01, right cerebellar tonsil, t(80)=6.38, p<0.001, pons, t(80)=6.79, p<0.001 and right posterior cingulate t(80)=5.90, p<0.001 in the ADHD group when compared to the normal controls. Results from the CPT-I, CCPT Index dichotomous variable, indicated that the ADHD group performed worse when compared to the non-psychiatric normal group, [c] (1, N=123) =15.63, p<0.001, during the concentration scan.

Conclusions: This may be the first neuro-imaging study that captures the brainstem as a possible anatomical structure in adult ADHD. Results from this study suggest that adult ADHD may involve deficits of the reticular activating system and the cerebellum. Pharmacological agents with a high affinity for the brainstem may innervate the catecholaminergic system to modulate arousal throughout the cortex in adults with ADHD and improve deficits of attention. 2

Source of Funding: None.

Literature References:
Randomized Placebo-Controlled Crossover Study of Acute Effect of Three Neuroactive Drugs Measured by Magnetoencephalography (MEG) and Electroencephalography (EEG)

Rajasimhan Rajagovindan, Ph.D., Michael Cassano, B.S., Jeffrey Lewine, Ph.D., Concetta Forchetti, M.D., Ph.D., Todd Verdoorn, Ph.D.

1 Orasi Medical, Inc., Minneapolis, MN, 2 Alexian Brothers Neuroscience Institute, Elk Grove Village, IL

Objective: This study was designed to measure and characterize how patterns of synchronous brain activity are specifically altered by administration of each of three neuroactive medications, with a goal of establishing templates of functional brain activity that are differentially associated with acute administration of each drug.

Methods: The study used a randomized, placebo-controlled crossover design to investigate the effect of modafinil (100 mg, p.o.), methylphenidate (20 mg, p.o.), and lorazepam (1 mg, p.o.) on brain activity in 15 healthy male volunteers. On each of four days, subjects received baseline magnetoencephalography (MEG) and electroencephalography (EEG) scans along with baseline cognition testing, with additional scans conducted at two, four and six hours after a single, oral dose of one of the three drugs or a placebo pill. One minute long resting-state profiles were analyzed separately over eight predefined groups of sensors using a regional variant of the Synchronous Neural Interaction test (SNI) and a standard frequency-domain approach, to detect and quantify drug-induced changes in brain activity.

Results: Lorazepam induced a global decrease in alpha activity (8–13 Hz) (p<0.001) and increase in delta activity (1–4 Hz) (p<0.002) compared to baseline, while simultaneously generating enhancements in SNI measured functional connectivity between frontal brain regions (p<0.008). Methylphenidate increased alpha activity over parietal, temporal and central regions (p<0.02) and decreased SNI between left frontal and left temporal areas (p<0.007). Modafinil increased alpha activity only in the parietal region (p<0.04). Drug-induced changes in behavioral measurements of reaction times and accuracy in simple cognitive testing were only marginally significant at α=0.05.

Conclusions: These results suggest that multivariate SNI and the frequency domain measures of brain activity are more sensitive to drug-induced changes in brain activity than conventional behavioral measures. Drug specific templates of functional changes in brain activity were observed using the two distinct measures of brain function.

Source of Funding: Orasi Medical, Inc.

Literature References:
Session I
Tuesday, June 15, 2010
12:00 p.m.–2:00 p.m.

Session I – 1  Withdrawn
Session I – 2  Early Adverse Events and Attrition in Selective Serotonin Reuptake Inhibitor (SSRI) Treatment: A Suicide Assessment Methodology Study (SAMS) Report
Diane Warden, University of Texas, Southwestern Medical Center
Madhukar Trivedi, Stephen Wisniewski, Benji Kurian, Sidney Zisook, Susan Kornstein, Edward Friedman, Sachiko Miyahara, Andrew F. Leuchter, Maurizio Fava, A. John Rush

Session I – 3  Prophylactic Efficacy of Fluoxetine, Escitalopram, Sertraline and Paroxetine in Unipolar Depression: Outcome after Long-Term Follow-Up
Rushaniya Khairova, Maimonides Medical Center
Eric Peselow, Rohit Pawar

Session I – 4  Gepirone Treatment of Generalized Anxiety Disorder (GAD)
Joseph DeVeaugh-Geiss, Duke University Medical Center

Session I – 5  The Mediation of Depression between Subjective Burden and Positive Aspects of Caring, and the Role of Antidepressants in Family Caregivers of Alzheimer’s Disease
Joanne DeVeaugh-Geiss, Walden University
Sylvia Bigatti

Session I – 6  Identifying Trajectories of Antipsychotic Treatment Response in Patients with Schizophrenia
Michael G. Case, Lilly USA, LLC
Virginia L. Stauffer, Haya Ascher-Svanum, Robert Conley, Shitij Kapur, John M. Kane, Sara Kollack-Walker, Jayanthi Jacob, Bruce J. Kinon

Session I – 7  Efficacy of Extended Release Quetiapine Fumarate (Quetiapine XR) MonoTherapy in Patients with Major Depressive Disorder (MDD): Pooled Analysis of Data for Patients with Different Levels of Baseline Disease Severity
Madhukar Trivedi, University of Texas, Southwestern Medical Center
Michael Thase, Stuart Montgomery, George Papakostas, Michael Bauer, Henrik Svedsater, Urban Gustafsson, Hans Eriksson

Session I – 8  Applying Discrete Choice Experiments in Mental Health – An Example on Parents’ Preferences in Attention Deficit Hyperactivity Disorder (ADHD) Treatment
Jörg M. Fegert, University Hospital Ulm
Lara Slawik, Matthias Nübling, Axel Mühlbacher

Session I – 9  Antidepressant-Placebo Differences over an Eleven Year Period in a Sample of Patients with High and Similar Baseline Scores
Arif Khan, Northwest Clinical Research Center
Amrits Bhat, James Faucett, Russell Kolts, Walter Brown

Session I – 10  Psychometric Properties of the Wender-Reimherr Adult Attention Deficit Disorder Scale
Fred Reimherr, University of Utah
Barrie K. Marchant, Reid J. Robison, Diane Robison, Paul Wender, Erika Williams, Corinne Halls, Douglas Kondo

Session I – 11  A Randomized, Controlled Clinical Trial Assessing the Effect of Guanfacine Hydrochloride on QT/QTC Interval in Healthy Adults
Lawrence Satin, Cardiocore
Patrick Martin, Gerald Tremblay, Jaideep Purkayastha

Session I – 12  Cardiovascular Safety of Stimulant Medications for Attention-Deficit Hyperactivity Disorder (ADHD): A Review of Data from Placebo-Controlled and Open-Label Extension Trials
Raul R. Silva, New York University, Langone Medical Center
Jeffrey W. Skimming, Rafael Muniz

Session I – 13  Withdrawn

Session I – 14  Effects of Stimulants on the Cerebellar Morphology in Attention Deficit Hyperactivity Disorder (ADHD)
Illyan Ivanov, Mount Sinai School of Medicine
Juan Sanchez-Pena, Ravi Bansal, Bradley Peterson

Session I – 15  A Study of the Coadministration of Guanfacine Extended Release and a Psychostimulant for the Treatment of Attention Deficit Hyperactivity Disorder: Design and Rationale
Timothy E. Willens, Massachusetts General Hospital, Harvard Medical School
Andrew Lyne, Sharon Youcha

Session I – 16  Pioglitazone for the Treatment of Bipolar Depression and Co-Occurring Insulin Resistance: Preliminary Evidence for Insulin Sensitization as a Novel Mechanism of Antidepressant Action
David E. Kemp, Case Western Reserve University
Faramarz Ismail-Beigi, Keming Gao, Elizabeth B. Fein, Carla M. Conroy, Sarah E. Obral, Philip K. Chan, Stephen J. Ganocy, Joseph R. Calabrese

Session I – 17  Predictors of Risperidone Serum Concentration in Youths
Chadi Calarge, University of Iowa
Eugene Arnold, Del Miller

Indicates New Investigator Awardee
Session I
Tuesday, June 15, 2010
12:00 p.m.–2:00 p.m.

Session I – 18  Dimensional and Categorical Measures of Personality Pathology in the Prediction of Treatment Outcome of Depression
Jessica Levenson, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center
Meredith Wallace, Jay Fournier, Paola Rucci, Ellen Frank

Session I – 19  Concise Associated Symptoms Tracking (CAST) Scale and Concise Health Risk Tracking (CHRT) Scale: Brief Self and Clinician Ratings of Suicidality and Associated Symptoms
Madhukar H. Trivedi, University of Texas, Southwestern Medical Center
David W. Morris, Stephen R. Wisneiwski, Maurizio Fava, Jackie Gollan, Andrew A. Nierenberg, Bradley N. Gaynes, Mustafa M. Husain, James F. Luther, Sidney Zisook, A. John Rush

Session I – 20  An Alternative Statistical Approach to Identifying Treatment-Responsive Classes in a Depression Trial
Maggie Kuchibhatla, Duke University Medical Center
Gerda G. Fillenbaum

Session I – 21  Theta-Burst Stimulation for the Treatment of Depression: Efficacy, Safety and Mechanisms
Moacyr A. Rosa, Columbia University
Charles Schroeder, Sarah Lisanby

Session I – 22  The Selective NK3 Antagonist AZD2624 Does Not Improve Symptoms or Cognition in Schizophrenia
Robert Litman, CBH Health, LLC
Mark Smith, Dhaaval Desai, Thomas Simpson, Stephen Kanes, Dennis Sweitzer

Session I – 23  Validation of a Laboratory Test to Aid in the Confirmation of Schizophrenia
Anthony Barnes, Rules-Based Medicine, Inc.
Mike Spain, James P. Mapes

Session I – 24  Persisting Racial Disparities Despite Increased Psychotropic Use across a Decade for Medicaid-Insured Youth
Julie M. Zito, University of Maryland, Schools of Pharmacy and Medicine
Aloysius Ibe, Daniel J. Safer, Laurence S. Magder

Session I – 25  Predictors of Response to Selective Serotonin Reuptake Inhibitors (SSRIs) in Premenstrual Dysphoria
Brooke G. Collins, National Institute of Mental Health
Steven M. Pincus, Graca Cordoso, David R. Rubinow, Peter J. Schmidt

Charles S. Wilcox, Pharmacology Research Institute
Ernest P. Noble, Nader Oskooiilar, Mellissa M. Henry, Terry L. Ritchie, Daniel E. Grosz, Barbara B. Katz, Jon F. Heiser

Session I – 27  Global Data Monitoring Program Reveals Significant Errors in the Administration and Scoring of Alzheimer’s Disease Assessment Scale-Cognitive Subscales (ADAS-COG)
Theresa A. Bromley, ePharmaSolutions
Marian A. Ormont

Session I – 28  Withdrawn

Session I – 29  The Economic Impact of Medication Access Problems
Joyce C. West, APIRE Psychiatric Practice Research Network
Donald C. Rae, Maritza Rubio-Stipec, Haiden Huskamp, Darrel A. Regier

Session I – 30  The Impact of Cortisol and Brain-Derived Neurotrophic Factor on Cognitive Function in Severe Depression
John Matthews, Massachusetts General Hospital
John W. Denninger, Larry Park, Caleb Siefert, Adrienne van Nieuwenhuizen, Rita Seabrook, Lauren House, Kaloyan Taney, David Abramson

Session I – 31  Metabolic Effects of Olanzapine in Children with Autistic Disorder
Richard P. Malone, Drexel University, College of Medicine
Susan H. West, Manely Ghaffari, Mary A. Delaney, Harold H. Hardison, Melissa Lech, Alicia Fuscellaro

Session I – 32  The Impact of Patients’ Expectations on Clinical Response: Re-Analysis of Data From the Hypericum Depression Trial Study Group
Justin Chen, Depression Clinical and Research Program, Massachusetts General Hospital
George Papakostas, Soo Yoon, Lee Baer, Alisabet Clain, Maurizio Fava, David Mischoulon

Session I – 33  The Implications of the Cognitive Deficit Profile in Schizophrenia for Therapeutic Strategies
Keith Wesnes, United BioSource Corporation
Howard Hassman, Helen Brooker, Chris Edgar, David Daniel
Session I
Tuesday, June 15, 2010
12:00 p.m.–2:00 p.m.

Session I – 34  Translational Development of Novel Pharmacotherapeutic Strategies for Psychostimulant Dependence
Steven T. Szabo, Duke University
Ashwin Patkar, Barry Mangum, Corey Fowler, Wayne F. Beyer, Joseph McClerndon, Bruce K. Burnett, David Gorenick, Tong H. Lee

Session I – 35  Using Motivational Interviewing to Supplement Online Training in Exposure Therapies for Naive Clinicians
Melanie Harned, Behavioral Tech Research
Linda Dimoff, Eric Woodcock

Session I – 36  Critical Time Intervention: Web-Based Dissemination of an Evidence-Based Practice
Jeff Olivet, Center for Social Innovation
Sam Catherine Johnston, Dan Herman, Sarah Conover, Suzanne Zerger

Session I – 37  NeuroVisions: Teaching Neuroscience with Neuroimaging Data
Steven Moore, Science Approach

Session I – 38  Brief Depression Screener Developed Using Item Response Theory (IRT) for Antenatal and Postpartum Women
Melanie Elliott Wilson, TeleSage, Inc.
Amy Brooks-DeWeese, Nora Doyle, Jacqueline Koble, Danielle Downing

Session I – 39  A Flexible, Web-Based System for the Administration of Computer Adaptive Tests
Robert Wirth, Vector Psychometric Group, LLC

Session I – 40  Utilizing Web-Based Education and Networking Tools to Enhance Geriatric Mental Health Research Mentoring and Career Management
Brian Shanahan, MediSpin, Inc.
Stephen J. Bartels, Martha Bruce, Jerden Unutzer, Gwenn Smith, Maureen Halpain, Barry D. Lebowitz, Charles F. Reynolds, Joel Streim

Session I – 41  Novel Vasopressin 1a Antagonists as Potential Drugs for Depression
Neal G. Simon, Azevan Pharmaceuticals, Inc.

Session I – 42  Comparing Mixed-Effect Model Repeated Measures (MMRM) versus Last Observation Carried Forward (LOCF) Statistical Methods in a Six-Week Placebo-and Active-Controlled Trial of Iloperidone for the Treatment of Schizophrenia
Peter J. Weiden, Center for Cognitive Medicine
Steven G. Potkin, Xiangyi Meng, Jason T. Olin

Session I – 43  The Effects of Olanzapine on QTc in Children with Autistic Disorder
Manely Ghaffari, Drexel University, College of Medicine
Susan H. West, Richard P. Malone, Harold H. Hardison, Mary A. Delaney, Melissa Lech, Alicia Fuscellaro

Session I – 44  A Pilot Study of Lamotrigine Adjunctive Therapy to Lithium and Divalproex in Depressed Patients with Rapid Cycling Bipolar Disorder and a Recent Substance Use Disorder: A 12-Week, Double-Blind Placebo-Controlled Trial
Keming Gao, Case Western Reserve University
Zuowei Wang, Dave E. Kemp, Philip K. Chan, Mary Beth Serrano, Calar Conroy, Yiru Fang, Stephen J. Ganocy

Session I – 45  Neurobehavioral Effects of Interferon-Alpha in Patients with Hepatitis C: Phenomenology and Paroxetine Responsiveness of Symptom Dimensions
Marcia McNutt, Emory University School of Medicine
Dominique Musselman, Erica Royster, Andrew Miller, Charles Raison

Session I – 46  Performance in Practice Clinical Tools for Post Traumatic Stress Disorder
Farifteh Duffy, American Psychiatric Institute for Research and Education
Thomas Craig, Eve Moscicki, Joyce West, Laura Fochtmann

Session I – 47  The Stanley Neuropathology Consortium Integrative Database: A Novel, Web-Based Tool for Exploring Molecular Targets for Therapeutic Drugs for Psychiatric Disorders and Pathways Associated with Those Targets
Sanghyeon Kim, Stanley Medical Research Institute
Maree Webster

Session I – 48  Possible Immunomodulatory Effects of Omega-3 Fatty Acids and Olive Oil in a 20-Week Clinical Trial of Children and Adolescents with Tourette's Disorder: Relationships to Treatment Response
Vilma Gabbay, New York University School of Medicine
Barbara Coffey, Yisrael Katz, Aviva Panzer, Carmen Alonso, James Babb

Session I – 49  Noninvasive Neuromodulation with Trigeminal Nerve Stimulation: A Novel Treatment for Major Depressive Disorder
Ian A. Cook, University of California, Los Angeles, Depression Research and Clinic Program, Semel Institute for Neuroscience and Human Behavior
Christopher M. DeGiorgio, Patrick R. Miller, Eve R. Maremont, Lara M. Schrader

Session I – 50  Association between Anxiety and Bipolar I Disorder in Randomized, Placebo-Controlled Maintenance Study of Ziprasidone Combined with Mood Stabilizer
Ketter A. Terence, Stanford University
Douglas Vanderburg, Elizabeth Pappadopoulous, Cynthia Siu, Onur Karayal
Session I
Tuesday, June 15, 2010
12:00 p.m.–2:00 p.m.

Session I – 51  Validation of an Electronic Columbia–Suicide Severity Rating Scale Using Interactive Voice Response Technology
John H. Greist, Alan J. Gelenberg, David J. Katzelnick, James W. Jefferson, Jack Modell

Session I – 52  Effect of Aripiprazole Adjunctive to Antidepressants on Sexual Functioning: A Subgroup Analysis of a 52-Week Open-Label Safety Study (CN138-164)
Anita H. Clayton, University of Virginia Health System
Ross A. Baker, Carlos Rojas-Fernandez, Robert A. Forbes, James Eudicone, Robert M. Berman

Session I – 53  Efficacy of Adjunctive Aripiprazole in Major Depressive Disorder (MDD) Patients with Minimal or Partial Response to Antidepressant Monotherapy
J. Craig Nelson, University of California, San Francisco
Michael E. Thase, Elizabeth E. Bellochio, Ross A. Baker, Linda M. Rollin, Robert D. McQuade, Ronald N. Marcus, Robert M. Berman

Session I – 54  Effect of a 12-Week Exercise Program on Serum Brain Derived Neurotrophic Factor (BDNF) in Major Depressive Disorder (MDD)
Marisa Toups, University of Texas, Southwestern Medical Center
Tracy Greer, Timothy Church, Madhukar H. Trivedi

Session I – 55  A Double-Blind, Placebo-Controlled Trial of Quetiapine for the Treatment of Mixed Hypomania in Bipolar II Disorder (BDII)
Trisha Suppes, Veterans Affairs Palo Alto Health Care System, Stanford University School of Medicine
Terence Ketter

Session I – 56  Double-Blind, Placebo-Controlled Efficacy and Safety Study of Lisdexamfetamine Dimesylate in Adolescents with Attention Deficit Hyperactivity Disorder (ADHD)
Ann Childress, Center for Psychiatry and Behavioral Medicine
Andrew Cutler, Maria Gasior, Mohamed Hamdani, M. Celeste Ferreira-Cornwell, Liza Squires, Robert Findling

Session I – 57  Electroconvulsive Therapy (ECT) Augmentation in Clozapine-Resistant Schizophrenia
Georgios Petrides, The Zucker Hillside Hospital, Northshore-Long Island Jewish Health System
Raphael J. Braga, Alan Mendelowitz, Samuel H. Balline, Nina Schooler, Max Fink

Session I – 58  Folate Supplementation in Schizophrenia
Kelsey J. Shannahah, Massachusetts General Hospital
Michele Hill, Sarah C. Jasinski, Eric A. Macklin, Lisa H. Raeke, Joshua L. Roffman, Donald C. Goff

Session I – 59  How to Assess the Speed of Antidepressant Effect: Insights from the Fixed Combination Pipamperone and Citalopram (PIPCIT) Clinical Trial Program
Kees Bol, Kinesis Pharma B.V.
Ludo Haazen, Erik Buntinx, Michael Thase

Session I – 60  A Pattern Recognition Matrix for Placebo-Response in Schizophrenia
Mark G.A. Opler, ProPhase LLC
Guillermo DiClemente

Session I – 61  Cross-Cultural Comparisons of American and Japanese Clinical Raters on Patients with Major Depressive Disorder Using the 17-Item Hamilton Rating Scale for Depression (HAM-D-17)
Graciete Lo, ProPhase LLC
Christian Yavorsky, Karen Tourian, Bruno Pitrosky, Linda Mele, Mark Opler, Ashleigh DeFries

Session I – 62  Treating Perinatal Depression in Low-Income Adolescents: Results from a Pilot Feasibility Study of Culturally Relevant, Brief Interpersonal Psychotherapy
Sarah E. Bledsoe, University of North Carolina, Chapel Hill
Amy Sommer, Abby Zeveloff, Anne-Marie Olarte

Session I – 63  Genotypic and Phenotypic CYP2D6 Poor Metabolizer Status among Outpatients with Depression Treated with Venlafaxine Extended Release
Cecelia Kane, Pfizer, Inc.
Alice Nichols, Vaisali Chhaya, Gina Buckley, Christine Guico Pabia

Session I – 64  Lurasidone Pharmacokinetics: Assessment of Potential for Drug-Drug Interactions
Sheldon Preskorn, University of Kansas School of Medicine, Wichita
Yu-Yuan Chiu, Donald Sarubbi, Masaaki Ogasa, Josephine Cucchiaro, Antony Loebel

Session I – 65  The Safety of Concomitant Use of Lorazepam Rescue in Treating Agitation with Inhaled Loxapine
Robert Fishman, Alexza Pharmaceuticals
Daniel Spyker, James Cassella

Session I – 66  Quantifying Rater Drift in an International Sample of Investigators Participating in Standardized Rater Training Events: Is Positive and Negative Syndrome Scale (PANSS) Reliability Maintained Over Time?
Christian Yavorsky, ProPhase LLC
Mark G.A. Opler, Evgenia Ivanova, Jessica Gordon, Sofija Jovic, Lisa Ramadhar, Larry Yang
Session I
Tuesday, June 15, 2010
12:00 p.m.–2:00 p.m.

Session I – 86  Factors Affecting Long-Term Lithium Compliance in Bipolar Illness
Eric D. Peselow, Maimonides Medical Center
Abiola Alao, Shannon Stepan, Neel Malhotra

Session I – 87  BI-1020, a GABA Enhanced Antipsychotic for the Treatment of Schizophrenia; Results of Phase 2b Effective Anti-Psychosis via GABA Level Enhancement (EAGLE) Trial
Yona Geffen, BioLineRx
Ravi Anand, Richard Keefe, Michael Davidson

Session I – 88  Baseline Characteristics of Patients with Schizophrenia Entered into Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC): An Intercontinental Large Simple Trial
John M. Kane, The Zucker Hillside Hospital and Albert Einstein School of Medicine
W. Wolfgang Fleischhacker, Jamie Geier, Cynthia Siu, Douglas Vanderburg, Onur N. Karayal, Robert Reynolds, Sybil Eng, Gerald Faich, Brian Strom

Session I – 89  Clozapine and Global Cognition in Schizophrenia
Tarek K. Rajji, Centre for Addiction and Mental Health
Hiroyuki Uchida, Zahinoor Ismail, Wenzie Ng, David Mamo, Gary Remington, Bruce G. Pollock, Benoit H. Mulsant

Session I – 90  A Comparison of Selective Serotonin Reuptake Inhibitors (SSRI) Treatment Effects in Major Depressive Disorder (MDD) Based on Three Different Clinician-Administered Depression Rating Scales
David J. Carpenter, GlaxoSmithKline
Regan Fong, Ole Graff, Suraja Roychowdhury, Susan M. Learned, Rachel P. Moate, John E. Kraus, Robert C. Alexander

Session I – 91  A Pooled Analysis of Data from Four Acute Studies in Major Depressive Disorders (MDD) to Assess the Effect of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy on Sleep Disturbance
Madhukar H. Trivedi, University of Texas, Southwestern Medical Center
Borwin Bandelow, Koen Demyttenaere, George I. Papakostas, Willie R. Earley, Johann Szamosi, Hans Eriksson

Session I – 92  Changes in Cognitive and Physical Function during Treatment with Low-Dose Aripiprazole Augmentation in Major Depressive Disorder
Daniosescu, Massachusetts General Hospital
Stella Bitran, Christina M. Dording, Michael Penci, Martina Flynn, Bijan Bastani, David Walling, John Zajecka, Mark H. Pollack, Maurizio Fava

Session I – 93  The Effect of Bipolar Disorder and Vascular Burden on Cognition in Elderly Adults
Ariel Gildeengers, University of Pittsburgh School of Medicine
Benoit Mulsant, Kari L. Seals, Rayan Al-Jurdi, John Beyer, Rebecca L. Greenberg, Laszlo Gyulai, Martha Sajatovic, Robert C. Young

Session I – 94  Response Trajectories during Citalopram Treatment for Major Depressive Disorder (MDD): Growth Mixture Modeling in the STAR*D Cohort
Aimee M. Hunter, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles
Bengt O. Muthen, Andrew F. Leuchter, Tihomir Asparouhov

Session I – 95  Withdrawn
Session II — 1
Instability of Serum Lithium Level/Dose Ratio Predicts Affective Episode Recurrence in Bipolar I Disorder
Alan G. Mallinger, National Institute of Mental Health, Intramural Research Program
Lobna Ibrahim, Ellen Frank, Michael E. Thase, David A. Luckenbaugh, David J. Kupfer

Session II — 2
Failure to Regulate Positive Emotions: A Functional Neuroimaging Approach to Emotion Dysregulation in Bipolar Disorder
June Gruber, Yale University

Session II — 3
Effects of Different Levels of Alcohol on Psychomotor and Cognitive Performance on the CogScreen Neuropsychological Test Battery
Gary Kay, Cognitive Research Corporation
Thomas Herbert Crook

Session II — 4
Bipolar Disorder Educational Needs in Primary Care
Jennifer L. Payne, Johns Hopkins University School of Medicine
Purvi K. Smith, Rachel DiPaolo

Session II — 5
Complementary Use of Tai Chi Improves Resilience, Quality of Life and Cognitive Function in Depressed Older Adults
Helen Lavretsky, University of California, Los Angeles
Michael Irwin

Session II — 6
Early Alliance in Prolonged Exposure and Sertraline for Chronic Post Traumatic Stress Disorder (PTSD)
Stephanie M. Pierce, Case Western Reserve University
Norah C. Feeny, Lori A. DiPaolo

Session II — 7
Effects of Cranial Electrotherapy Stimulation on Resting Brain Activity
Jamie Feusner, University of California, Los Angeles
Teena Moody, Emily Hembacher, Susan Bookheimer, Alexander Bystritsky

Session II — 8
Monitoring Social Behavior Using the Child Conflict Index in Children with Attention Deficit Hyperactivity Disorder (ADHD) Treated with OROS Methylphenidate
Harriette L. Starr, Ortho-McNeil Scientific Affairs, LLC
Norah C. Feeny, Lori A. DiPaolo

Session II — 9
Late-Day Attention Deficit Hyperactivity Disorder (ADHD) Symptom Control Improvement with Extended-Release Dexmethylphenidate in Children with ADHD of All Ethnicities: A Sub-Analysis
American Padilla, Miami Children's Hospital
Lind慢慢 Pestrinck, Kevin McCague, Rafael Muniz

Session II — 10
Withdrawn

Session II — 11
Withdrawn

Session II — 12
Extended-Release Dexmethylphenidate 30 mg Improves Late-Day Attention Deficit Hyperactivity Disorder (ADHD) Symptom Control in Children with ADHD: A Randomized, Double-Blind Crossover Study
Rafael Muniz, Novartis Pharmaceuticals Corporation
Lind慢慢 Pestrinck, Kevin McCague, Americo Padilla, Matthew Brams, Ann Childress

Session II — 13
The Efficacy of Once-Daily Trazodone in Major Depressive Disorder is Independent of Baseline Sleep Status or Depression Severity
Michael Gibertini, INC Research, Inc.
Anna Rozova, E. Roderich Gossen

Session II — 14
Fronto-Limbic Connectivity in Adolescents with Depression
Kathryn Cullen, University of Minnesota Medical School
Kelvin O. Lim, Bonnie Klimes-Dougan

Session II — 15
Psychiatry Resident/Fellow Initiated and Designed Multi-Modal Psychopharmacology Curriculum in Major Depression
Kristina M. Deligiannidis, University of Massachusetts Medical School
Ragy R. Girgis, Deepak Prabhakar, Emily Gastelum, Adam Lau, Bernadette Stevenson, Amy K. Ricke, Carolyn Broudy, Kartic Rajput, Vinay Saranga, Joshua Kayman, Richard Balon, Sidney Zisook

Session II — 16
Effect of Food on Lurasidone Absorption
Yu-Yuan Chiu, Dainippon Sumitomo Pharma
Sheldon Preskorn, Donald Sarubbi, Josephine Cucchiaro, Antony Loebel

Session II — 17
GLYX-13, an NMDA Receptor Glycine Site Functional Partial Agonist, Does Not Elicit Psychotomimetic Side Effects in Normal Human Volunteers at Doses Expected to Be Therapeutic in Treatment-Resistant Major Depressive Disorder
Ronald M. Burch, Naurex, Inc.
Neil Singla

Indicates New Investigator Awardee
Session II
Wednesday, June 16, 2010
12:15 p.m.–2:15 p.m.

Session II – 18 In-Depth Analysis of Short-Term Tolerability of Desvenlafaxine 50 mg/d in Patients with Major Depressive Disorder
Cecelia Kane, Pfizer, Inc.
Robert Northington, Sujana Reddy,
Christine J. Guico Pabia, Philip T. Ninan

Session II – 19 An Assessment of the Pharmacokinetics and Tolerability of Single Ascending Doses of Desvenlafaxine Administered to Healthy Chinese Subjects
Alice Nichols, Pfizer, Inc.
Lingling Guan, Madelyn Abell, Glen Frick

Session II – 20 Assessing Motivation in Schizophrenia
Fabien Tremeau, Nathan Kline Institute,
New York University
Karen Nolan, Daniel Javitt

Session II – 21 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)
Maurizio Fava, Massachusetts General Hospital
David Mischoulon, Dan Iosifescu, Janet Witte,
Michael Pencina, Martina Flynn, Linda Harper,
Michael Levy, Karl Rickels, Mark Pollack

Session II – 22 Efficacy of Extended Release Quetiapine Fumarate (Quetiapine XR) in Patients with Major Depressive Disorder (MDD): Results from Eight Double-Blind Randomized Studies
Stuart Montgomery, Imperial College School Of Medicine
Amir Kalali, Willie Earley, Johan Szamosi,
Hans Eriksson

Session II – 23 Effects of Dextro-Amphetamine on Cortical Oscillations in Schizophrenia versus Healthy Control Subjects
Raymond Cho, University of Pittsburgh
Christopher Walker, RyAnna Verbiest,
William G. Frankle, David Lewis

Session II – 24 Quetiapine XR as Adjunct to Antidepressants in Patients with Major Depressive Disorder (MDD) and Inadequate Response to Therapy: Pooled Analysis of Data for Patients with Low and High Levels of Baseline Anxiety
Nizar El-Khalili, Alpine Clinic
Borwin Bandelow, Eduard Vieta, Urban Gustafsson,
Hans Eriksson

Session II – 25 Impact of Information Demands on Site versus Expert Inter-Rater Reliability of the Positive and Negative Syndrome Scale (PANSS)
Bethanne Friedmann, Worldwide Clinical Trials
Michael Murphy, Neal Cutler, Henry Riordan

Session II – 26 Inter-Rater Reliability in the Assessment of Pediatric Schizophrenia Using the Positive and Negative Syndrome Scale (PANSS): Training Results from a Russian Cohort
Mark Opler, ProPhase LLC
David Hough, Diane Hoffman,
Evgenia Ivanova, Christian Yavorsky,
Stacy Liechti, Gil Zalsman

Session II – 27 Placebo Response in Anti-Psychotic Trials
Cynthia Siu, DataPower, Inc.
Ofer Agid, Gary Remington, Shitij Kapur,
Eric Watsky, Douglas Vanderburg,
Steven G. Potkin

Session II – 28 Trial Level Meta-Analysis of Duloxetine Efficacy on Painful Physical Symptoms in Major Depressive Disorder for Patients with Clinically Significant Painful Physical Symptoms at Baseline
Durisala Desaiab, Eli Lilly and Company
Susan G. Ball, Melissa E. Spann, James M. Russell,
Michael J. Robinson

Session II – 29 Divalproex Sodium (DVG) for the Treatment of Impulsivity and Aggression in Connecticut Prisons
Jayesh Kamath, University of Connecticut Health Center
Humberto Temporini, Karen Kesten,
Wanli Zhang, Sue Quarti, Nicholas Demartinis,
Robert Trestman

Session II – 30 Effect of Adjunctive Aripiprazole on Domains of Functioning in Patients with Major Depressive Disorder: A Pooled Analysis of Three Clinical Trials
Zachary J. Cain, Bristol-Myers Squibb
Tanya J. Fabian, Linda M. Rollin, Robert A. Forbes,
Robert M. Berman, Ross A. Baker

Session II – 31 Does Sponsorship Influence Dosing in Randomized Controlled Trials of Antidepressants for Major Depressive Disorder? A Meta-Analysis
Mark Sinyor, University of Toronto, Ontario
Ayal Schaffer, Kelly Smart, Anthony Levitt,
Krista Lantct

Session II – 32 Analysis of Baseline Characteristics of Major Depressive Disorder Patients Treated with Antidepressant Therapy: A Pooled Analysis of Three Studies
Madhukar H. Trivedi, University of Texas,
Southwestern Medical School
William R. Clark, Sabrina Vogel Marler,
Robert A. Forbes, Ross A. Baker

Session II – 33 Efficacy and Safety of Adjunctive Aripiprazole in Combination with Lamotrigine in a Long-Term Maintenance Study in Manic Or Mixed Subjects with Bipolar I Disorder (CN138-392)
Berit Carlson, Bristol-Myers Squibb
Wei Sun, Karen Timko, Estelle Vester-Blokland,
Robert McQuade, Raymond Sanchez,
Randall Owen

Session II – 34 Rapid Improvement in the Five-Item Positive and Negative Syndrome—Excited Component (PANSS-EC) Scale for Agitation with Inhaled Loxapine
James Cassella, Alexza Pharmaceuticals
Daniel Spyker, Joseph Kventus, Michael Lesem,
Robert Fishman
Session II
Wednesday, June 16, 2010
12:15 p.m.–2:15 p.m.

Session II – 35  Aripiprazole Partial Agonism at 5HT2c: A Comparison of Weight Gain Associated with Adjunctive Aripiprazole to Antidepressants with High versus Low Serotonergic Activities
Charles Nguyen, Veterans Affairs, Long Beach Healthcare System
Jennifer Rosen, Michael Juzba

Session II – 36  Withdrawn

Session II – 37  Assessment of Spontaneous and Evoked Gamma Oscillations by Quantified Electroencephalograph (EEG), a Potential Biomarker of Glutamatergic Transmission: Methodological Issues in Humans, Descriptive Data and Test-Retest Reliability
Remy Luthringer, FORENAP Pharma
Jim Fergusson, Peter Boeijinga, Nathalie Pross, Corinne Staner, Laurent Soufflet, Damien Maurice, Geoffrey Viardot, Philippe Danjou

Session II – 38  Partial Response to Antidepressant Monotherapy Predicts Remission: Results from the Aripiprazole Clinical Trial Program in Major Depressive Disorder
Michael E. Thase, University of Pennsylvania School of Medicine

Session II – 39  Rater Training on Hamilton Rating Scale for Depression (HAM-D), Montgomery Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS)—What Were the Difficult Items to Rate?
Richa Gaur, The Cognition Group
Martha Sajatovic, Nathan Lee, Luis Ramirez, Geetika Nath, Hossein Kaviani

Session II – 40  Associations between Child Behavior Checklist Profiles and Candidate Genes in Adolescent Bipolar Disorder
Victoria E. Cosgrove, Stanford University School of Medicine
David J. Miklowitz, Christopher Hawkey, Elizabeth L. George, Dawn O. Taylor, Lindsey L. Gagnon

Session II – 41  Ratings of Manic Psychopathology in Geriatric Bipolar Patients: An Acute Pharmacotherapy of Late-Life Mania (Geri-BD) Report
Laura Davan, Weill Medical College of Cornell University
Martha Sajatovic, Ariel Gildengers, Benoit Mulsant, Laszlo Gyulai, John Beyer, Ryan Al Jurdi, Mark Kunik, Ricky Greenberg, Patricia Marino, Javier Evans, Robert Young

Session II – 42  Conversion of Lisdexamfetamine Dimesylate to Active d-Amphetamine
Michael Pennick, Shire Pharmaceutical Development Ltd.

Session II – 43  Indoleamine-Dioxygenase Activity is Associated with Psychiatric and Clinical Outcomes in Patients with Coronary Artery Disease
Walter Swardfager, Sunnybrook Health Sciences Centre
Nathan Herrmann, Mahwesh Saleem, Paul I. Oh, Scott E. Walker, Marilyn Sherman, Krista L. Lantot

Session II – 44  Effect of Language-Specific Training on Rater Performance in Assessment of Positive and Negative Syndrome Scale (PANSS) Items and Subscales
Stacy Liechti, ProPhase LLC
Jessica Gordon, Evgenia Ivanova, Sofija Jovic, Lisa Ramadhar, Mark Opler, Christian Yavorsky

Session II – 45  Efficacy of Lurasidone in Schizophrenia: Summary of Results from the Clinical Development Program
Antony Loebel, Dainippon Sumitomo Pharma Josephine Cuccionari, Masaaki Ogasa, Robert Silva, Andrei A. Pikalov, Jay Hsu, Jane Xu

Session II – 46  Pooled Analysis of the Efficacy of Desvenlafaxine 50 mg Compared with Placebo in the Patients with Moderate or Severe Major Depressive Disorder
Christine J. Guico Pabia, Pfizer, Inc.
Jeff Musgnung, Ben Wang

Session II – 47  Milnacipran Improves Pain, Patient Global Impression of Change (PGIC), Physical Function and Depressive Symptoms in Fibromyalgia: Results from a Placebo-Controlled Milnacipran Trial
Lesley M. Arnold, University of Cincinnati College of Medicine
R. Michael Gendreau, Judy Gendreau, Allan Spera, Yong Wang, Ian D’Souza

Session II – 48  Post-Hoc Endpoint Readjudication of the Secondary Sudden Death Endpoint per International Classification of Diseases (ICD) 10 Coding in the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) Trial
Onur Karayal, Pfizer, Inc.
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The Effects of Nicotine Patch on Cognitive Domains Identified by Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) in Nicotine Abstinent Adults with Chronic Schizophrenia

Sohi, Manmohandeep
An Open-Label, Rater Blinded Six-Week Pilot Trial of Escitalopram for Generalized Anxiety Disorder Among Patients with Human Immunodeficiency Virus (HIV)

Starr, Harriette
Monitoring Social Behavior Using the Child Conflict Index in Children with Attention Deficit Hyperactivity Disorder (ADHD) Treated with OROS Methylphenidate

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Efficacy of Valproic Acid, Lithium Carbonate and Carbamazepine in Maintenance Phase of Bipolar Disorder—A Naturalistic Study

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Can Mild-Moderate Depression Benefit from Antidepressant Medication?

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Impairment in Psychosocial Functioning Associated with Dysthymic Disorder in the Natural Epidemiologic Study of Alcoholic Related Conditions (NESARC) Study

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Do Recruitment Sources Impact Study Outcome: Assessment by Computer and Site-Based Raters

Suppes, Trisha
A Double-Blind, Placebo-Controlled Trial of Quetiapine for the Treatment of Mixed Hypomania in Bipolar II Disorder (BDII)

Swardfager, Walter
Indoleamine-Dioxygenase Activity is Associated with Psychiatric and Clinical Outcomes in Patients with Coronary Artery Disease

Szabo, Steven
Translational Development of Novel Pharmacotherapeutic Strategies for Psychostimulant Dependence

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Relationship between Probability of Receiving Placebo and Probability of Prematurely Discontinuing Treatment in Double-Blind, Randomized Clinical Trials for Major Depressive Disorder (MDD): A Meta-Analysis

Terence, Ketter
Association between Anxiety and Bipolar I Disorder in Randomized, Placebo-Controlled Maintenance Study of Ziprasidone Combined with Mood Stabilizer

Thase, Michael
Efficacy of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy in Patients with Major Depressive Disorder (MDD): Pooled Analysis of Data for Patients with Different Levels of Baseline Disease Severity

Indicates New Investigator Awardee
Thase, Michael
Partial Response to Antidepressant Monotherapy Predicts Remission: Results from the Aripiprazole Clinical Trial Program in Major Depressive Disorder

Toups, Marisa
Effect of a 12-Week Exercise Program on Serum Brain Derived Neurotrophic Factor (BDNF) in Major Depressive Disorder (MDD)

Tremeau, Fabien
Assessing Motivation in Schizophrenia

Tripp, Adam
Altered Somastatin (SST) and Nerve Growth Factor Inducible (VGF) Gene Expression in Anterior Cingulate Cortex of Post-Mortem Human Subjects with Recurrent Major Depression

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A Pooled Analysis of Data from Four Acute Studies in Major Depressive Disorder (MDD) to Assess the Effect of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy on Sleep Disturbance

Trivedi, Madhukar
Analysis of Baseline Characteristics of Major Depressive Disorder Patients Treated with Antidepressant Therapy: A Pooled Analysis of Three Studies

Turkoz, Ibrahim
Reporting Adverse Event Data from Clinical Trials of Antipsychotic Agents

Vaishnavi, Sandeep
Patients with Late-Life Depression Have Impairment on Neurocognitive Tests Sensitive and Specific for Dementia

Vanderburg, Douglas
Predictive Function of Treatment Outcomes in Patients with Schizophrenia

Warden, Diane
Early Adverse Events and Attrition in Selective Serotonin Reuptake Inhibitor (SSRI) Treatment: A Suicide Assessment Methodology Study (SAMS) Report

Weber, Christopher
The MedAvante Analysis of Rating Quality- Alzheimer’s Disease (MARQ-AD): A New Measure of Interview Quality in Alzheimer’s Disease Trials

Weiden, Peter
Comparing Mixed-Effect Model Repeated Measure (MMRM) versus Last Observation Carried Forward (LOCF) Statistical Methods in a Six-Week Placebo- and Active-Controlled Trial of Iloperidone for the Treatment of Schizophrenia

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The Implications of the Cognitive Deficit Profile in Schizophrenia for Therapeutic Strategies

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Biomarkers and Expediting Drug Development: An Interim Report on the Molecular Genetic (DRD2) Basis of Nicotine Addiction and Treatment Response

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A Study of the Coadministration of Guanfacine Extended Release and a Psychostimulant for the Treatment of Attention Deficit Hyperactivity Disorder: Design and Rationale

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Placebo Response Assessed by Site and Blinded Remote Centralized Raters in a Generalized Anxiety Disorder (GAD) Trial

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A Flexible, Web-Based System for the Administration of Computer Adaptive Tests

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Critical Time Intervention: Web-Based Dissemination of an Evidence-Based Practice

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A Web-Based System for Measuring Outcome in the Treatment of Depression: Reliability, Validity and Patient Acceptance

Zito, Julie
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