NCDEU

An Annual Meeting of the ASCP

Recognizing Unmet Needs in Psychopharmacology: From Biomarkers to Breakthrough Therapies

ORAL ABSTRACTS

MAY 28 – 31, 2013

NCDEU
New Research Approaches
for Mental Health Interventions

ASCP
AMERICAN SOCIETY OF
CLINICAL PSYCHOPHARMACOLOGY

Tuesday, May 28, 2013

PANEL
9:00 AM – 10:30 AM
PANEL OVERVIEW:
FROM THE DETECTION AND DIAGNOSIS TO THE PREVENTION AND
TREATMENT OF POSTTRAUMATIC STRESS DISORDER

Lori L. Davis, M.D.[1], Lori L. Davis, M.D.[1], Bradley Gaynes, M.D., MPH[2], Barbara Rothbaum, Ph.D.[3]
[1]University of Alabama School of Medicine, [2]University of North Carolina, [3]Emory University School of Medicine

In keeping with the 2013 NCDEU theme "Recognizing Unmet Needs in Psychopharmacology: From Biomarkers to Breakthrough Therapies," this 90-minute panel will present 1) review of the randomized controlled trials of psychotherapy and pharmacotherapy for the treatment of posttraumatic stress disorder (PTSD) that may be used to inform future research aims (B. Gaynes), 2) the cutting edge findings on biomarkers as predictors of illness and outcome that may be used to define new therapeutic approaches (B. Rothbaum), and 3) how the new DSM-5 criteria and novel functional outcome measures for PTSD may impact clinical trial design (L. Davis).

Learning Objectives:
- After the attending the panel, the participant will be able to state the treatments that have shown some positive evidence in the treatment of PTSD.
- The participant will recognize important biomarkers that may be possible indicators of illness, severity, and treatment response.
- The participant will understand the newly proposed DSM5 diagnostic criteria for PTSD. The participant will recognize important functional domains that may be outcome targets for treatment studies.

INDIVIDUAL ABSTRACT:
PSYCHOLOGICAL AND PHARMACOLOGICAL TREATMENTS FOR ADULTS
WITH POSTTRAUMATIC STRESS DISORDER: WHAT DOES THE EVIDENCE
SHOW?

Bradley Gaynes, M.D., MPH
University of North Carolina

The estimated lifetime prevalence of posttraumatic stress disorder (PTSD) among adults in the United States is 6.8 percent with current prevalence estimated at 3.6%. Recent surveys of military personnel have yielded estimates ranging from 6.2 percent for U.S. service members who fought in Afghanistan to 12.6 percent for those who fought in Iraq. Many people with PTSD never receive treatment: less than half of individuals who screened positive for PTSD after serving with the US military in Iraq or Afghanistan were referred for further evaluation or treatment, and of these, only 65% received care. Even those receiving care face a challenge; guidelines for the management of PTSD have disagreed about the effectiveness of treatments, leading to different recommendations about broad categories of treatment and the effectiveness of specific treatments that fit into these broad categories. Dr. Gaynes will systematically review the current evidence base for the use of psychological and pharmacologic treatments for adults for PTSD and discuss how this data informs the disorder's future research needs.

Learning Objectives:
- To systematically review the evidence addresssing the effectiveness of psychological treatments for PTSD
- To systematically review the evidence addresssing the effectiveness of psychotropic treatments for PTSD

Literature References:
- Committee on Treatment of Posttraumatic Stress Disorder, Institute of Medicine. Treatment of PTSD: assessment of the evidence. Washington, DC: National Academies Press; 2008.
- Forbes D, Creamer M, Bisson JI, et al. A guide to guidelines for the treatment of PTSD and related conditions. J Trauma Stress. 2010 Oct;23(5):537-52. PMID: 20839310

INDIVIDUAL ABSTRACT:
BIOMARKERS AND THEIR USE IN THE DETECTION AND TREATMENT OR PREVENTION OF PTSD
Barbara Rothbaum, Ph.D.
Emory University School of Medicine

Current research in biomarkers of the detection, prevention, and treatment of PTSD has expanded to include genetic markers and immunocytokines. One mechanism that may contribute to the development of anxiety, depression, and hyperarousal in patients with PTSD is inflammation. Patients with depression and anxiety disorders, including PTSD, reliably exhibit increases in inflammatory markers. Administration of inflammatory cytokines and their inducers has been shown to cause symptoms of anxiety, hyperarousal and depression. In addition, inflammatory cytokines interact with nearly every pathophysiologic domain relevant to depression and anxiety including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and activity in relevant brain regions such as the anterior cingulate cortex and the basal ganglia. Recent data suggest that blockade of cytokines or their signaling pathways can reduce symptoms of anxiety and depression in both patients with autoimmune and inflammatory disorders as well as patients with major depression. One of the primary systemic regulators of the cellular inflammatory response is cortisol. Individuals with the "risk" FKBP5 genotypes associated with glucocorticoid responses were more likely to develop adult PTSD if they had experienced childhood sexual or physical abuse. Another 'risk' allele, PACAP Receptor (ADCYAP1R1, rs2267735) polymorphisms, genes associated with stress-response, has been associated with higher PTSD symptoms in emergency room trauma patients who received assessment only compared than those who received intervention or those with the 'non-risk' allele at 4 and 12 weeks. This same pattern held when the 10 genes were combined to assess a genetic risk profile. PTSD symptoms were correlated with level of genetic risk at week 4 ($p<0.05$) and week 12 ($p<0.005$) in the assessment-only group, but with no relationship in the intervention group. This held even after controlling for age, sex, race, education, income, and childhood trauma. Having 4 or more of the high-risk alleles was associated with a significantly greater likelihood of being diagnosed with PTSD at 12 weeks in the assessment group only ($p=0.002$). Thus, genetic risk/resilience polymorphisms may serve to identify those who are most at risk for developing PTSD in the aftermath of trauma, and a psychotherapeutic intervention initiated within hours of the trauma is successful at mitigating this risk.

Learning Objectives:
- Understand some of the biomarkers that may indicate for PTSD

- understand some of the biomarkers for PTSD that may indicate treatment response

Literature References:
- Binder, E., Bradley, R., Liu, W., Epstein, M., Deveau, T., Mercer, K., Tang, y., Gillespie, C., Heim, C., Nemeroff, C., Schwartz, A., Cubells, J., Ressler, K. (2008) FKBP5 Polymorphisms Moderate Effects of Child Abuse on Risk for PTSD in Adults. Journal of the American Medical Association, Mar 19;299(11):1291-305.
- Ressler, K., Mercer, K., Bradley, B., Jovanovic, T., Mahan, A., Kerley, K., Norrholm, S. (2011). Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature, 470, 492-497.
- Mehta D, Gonik M, Klengel T, Rex-Haffner M, Menke A, Rubel J, Mercer KB, Pütz B, Bradley B, Holsboer F, Ressler KJ, Müller-Myhsok B, Binder EB. Using polymorphisms in FKBP5 to define biologically distinct subtypes of posttraumatic stress disorder: evidence from endocrine and gene expression studies. Arch Gen Psychiatry. 2011 Sep;68(9):901-10. doi: 10.1001/archgenpsychiatry.2011.50. Epub 2011 May 2. PubMed PMID: 21536970.

INDIVIDUAL ABSTRACT:
DIAGNOSTIC CRITERIA AND OUTCOME TARGETS FOR PTSD IN CLINICAL TRIALS DESIGN
Lori L. Davis, M.D.
University of Alabama School of Medicine
The rational and revision of DSM diagnostic criteria for PTSD will be discussed. The anticipated impact of the DSM-5 revisions on rating scale structure and treatment targets in clinical trials design will be explored. Given the heterogeneity of PTSD clinical presentations and the diverse functional outcomes of the illness trajectory, perhaps identifying biomarkers to enable a more refined or enriched participant sample would led to a better differentiation between intervention versus control group responses. Novel treatment paradigms aimed at a reliable outcome target within a participant sample paired with a candidate biomarker inclusion criterion may led to more efficient clinical trial design.

Learning Objectives:
- The participant will understand the newly proposed DSM5 diagnostic criteria for PTSD and the implication in clinical trial design.
- The participant will recognize important functional domains that may be outcome targets for treatment studies.

Literature References:
- Friedman MJ, Resick PA, Bryant RA, Brewin CR. Considering PTSD for DSM-5. Depress Anxiety. 2011 Sep;28(9):750-69.
- Leon AC, Davis LL. Enhancing clinical trial design of interventions for posttraumatic stress disorder. J Trauma Stress. 2009 Dec;22(6):603-11.

GENERAL DISCUSSION
Lori L. Davis, M.D.
University of Alabama School of Medicine

PANEL
9:00 AM – 10:30 AM

PANEL OVERVIEW:
IDENTIFYING AND MANAGING EMERGING MEDICAL COMORBIDITIES IN EARLY MENTAL ILLNESS

Benedetto Vitiello, M.D.[1], Christoph U. Correll, MD[2], Delbert Robinson, M.D.[3], John W. Newcomer, M.D.[4], John W. Newcomer, M.D.[4], Charles H. Hennekens, M.D.[5]
[1]NIMH, [2]Hofstra North Shore LIJ School of Medicine, [3]Hofstra North Shore-LIJ School of Medicine at Hofstra University, [4]Miller School of Medicine, University of Miami, [5]Florida Atlantic University

People with severe mental illness (SMI) die prematurely from the same leading causes of death that affect the general population – e.g., coronary heart disease (CHD), cerebrovascular disease, diabetes, pulmonary disease – with higher mortality at younger ages contributing to marked reductions in life expectancy. On average, adults with psychotic disorders die 11-32 years earlier than adults with no mental disorder, most often from CHD as well as these other medical conditions. Modifiable cardiometabolic risk factors that contribute to early mortality—smoking, obesity, hypertension, dyslipidemia, pre-diabetes —are more common among people with SMI, and often appear at earlier ages. This panel will explore risk factors for premature death that can be present at the time of psychosis onset, how antipsychotic medications can increase medical risks among children, adolescents and adults with early mental illness, and how computer-based decision tools can assist in early identification and management of co-morbid medical problems in vulnerable patients. The panel will consist of three talks, followed by a discussion and general audience participation.

Learning Objectives:
- Following this presentation, audience members will be able to list 3 co-morbid medical conditions associated with premature death in SMI and 3 modifiable risk factors that contribute to early mortality.
- Following this presentation, audience members will be able to list 2 ways in which antipsychotic medications may increase medical risk and 2 ways in which these risks can be managed.

INDIVIDUAL ABSTRACT:
RISK FACTORS FOR MEDICAL CO-MORBIDITIES OBSERVED AT THE ONSET OF PSYCHOSIS

Christoph U. Correll, M.D.
Hofstra North Shore LIJ School of Medicine

Background: Patients with schizophrenia have increased cardiovascular risk factors and an average 15-25 year shorter lifespan than the general population. However, reasons for this enhanced risk are complex, involving illness related factors, unhealthy lifestyle, treatment-related adverse cardiometabolic effects, and suboptimal medical monitoring/care. Identifying risk factors at illness onset and following patients over time is the best strategy to elucidate mediating and moderating variables.
Method: As part of the NIMH-funded, cluster-randomized Recovery After an Initial Schizophrenia Episode (RAISE) study, we examined physical and, especially, cardiovascular health status and medical treatment at baseline, aiming to follow trajectories in the usual care and enhanced treatment groups during this ongoing study. RAISE subjects, aged 15-40 years with a first episode schizophrenia-spectrum disorder and 6 months or less of lifetime antipsychotic

treatment, underwent baseline screening for medical morbidity, anthropometric assessments, and glucose and lipid testing.

Results: 404 subjects (72.5% male, median age: 22 years) entered the study. All but 40 patients (9.9%) received medication treatment at baseline, including antipsychotics (85.9%, of which 89.9% were second-generation antipsychotics). The mean body mass index of this young patient sample was 25.5±8.8 and 48.7% were either obese (21.2%) or overweight (27.5%) but only 4.1% of patients had arterial hypertension. However, hypercholesterolemia was present in 20.7%, hypertriglyceridemia in 22.0% of patients. Hemoglobin A1C-determined hyperglycemia was present in 13.3% and diabetes mellitus in 2.2% of first episode patients. Cardiovascular risk factor frequencies will be compared in detail to those in the general US population and other first episode samples. Data on moderators and mediators of cardiovascular risk status including their relationship to demographic, illness and antipsychotic treatment type and duration, will also be available at the time of the meeting.

Discussion: After less than 6 months of antipsychotic treatment, half of first episode schizophrenia-spectrum disorder patients were obese or overweight, one in five had hypercholesterolemia and hypertriglyceridemia and one in seven patients had either prediabetes or diabetes. These risk factor frequencies are higher than expected in a sample with a median age of 22 years. Cardiometabolic risk trajectories need to be examined as early as possible after antipsychotic treatment initiation. Cardiometabolic risk factor monitoring and adequate management are essential to improve the short- and long-term health of first episode schizophrenia-spectrum disorder patients.

Learning Objectives:
- Identify cardiometabolic risk factors in patients with first episode psychosis
- Recognize risk and protective factors for cardiometabolic health
- Apply appropriate risk identification and minimization strategies in seriously mentally ill patients

Literature References:
- De Hert M, Correll CU, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011 Feb; 10(1)52-77.
- De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011 Oct 18;8(2):114-26.

INDIVIDUAL ABSTRACT:
PHASE-SPECIFIC PHARMACOTHERAPY FOR FIRST EPISODE PSYCHOSIS
Delbert Robinson, M.D.
Hofstra North Shore-LIJ School of Medicine at Hofstra University
Background: Research studies of first episode schizophrenia have consistently found high rates of treatment response with low dose antipsychotic treatment but also high rates of metabolic and other side effects. How much these data influence treatment practices outside academic centers is unknown as data on current community center treatment is lacking. Method: We examined current antipsychotic treatment practice within the context of the RAISE-ETP study, a randomized comparison of NAVIGATE, an integrated treatment program, and usual care performed at 34 community facilities in 21 different US states. The ETP study enrolled subjects aged 15 to 40 years with a first episode schizophrenia-spectrum disorder and 6 months or less of

cumulative antipsychotic treatment. Results: 404 subjects (292 men and 112 women; median age 22 years) entered the study. 40 were not prescribed any medications at the time of study entry; 2 were prescribed only medications for medical problems; 15 were prescribed only psychotropics other than antipsychotics and 347 were prescribed antipsychotics. 304 of the 347 were prescribed only 1 antipsychotic [276 a second generation agent (SGA) and 28 a first generation agent (FGA)] and 43 were prescribed multiple antipsychotics (29 were prescribed 2 SGAs and 1 three SGAs; 13 were prescribed combinations of SGAs and FGAs). The 5 most commonly prescribed antipsychotics were: risperidone 33% of all antipsychotic prescriptions; olanzapine 16% of prescriptions; quetiapine 11%; aripiprazole 11% and paliperidone 10%. The 2009 PORT recommendations provides guidance about dose ranges for first episode treatment with risperidone, a first-line PORT medication, and for olanzapine, a medication not recommended for first-line use by PORT. The suggested ranges are the lower half of the multi-episode daily dose ranges of 2-8mg for oral risperidone and 10-20 mg for oral olanzapine. Median daily dose of risperidone for ETP patients was 3 mg and 15 mg for olanzapine. 21% of olanzapine prescriptions but none of the risperidone prescriptions were for doses higher than the PORT range for multi-episode patients.

Discussion: Some current community treatment practices may increase the risk of metabolic side effects with first episode patients. Globally, SGAs are used in preference to FGAs. The use of multiple antipsychotics is high given that the target population is relatively treatment responsive and the relatively frequent use of olanzapine in early treatment, especially at high doses, is notable. Navigate treatment includes COMPASS, a web-accessed medication decision support system. COMPASS components that minimize health risks related to schizophrenia treatments will be presented at the meeting.

Learning Objectives:
- Following this presentation, audience members will be able to describe the COMPASS system for medication treatment of first episode schizophrenia spectrum disorders.
- Following this presentation, audience members will be able to describe the COMPASS system for medication treatment of first episode schizophrenia spectrum disorders.

Literature References:
- Robinson DG, Woerner MG, Napolitano B, et al. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. Am J Psychiatry. 2006;163(12):2096–2102.
- Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements. Schizophrenia Bulletin. 2010;36(1):71 –93.

INDIVIDUAL ABSTRACT:
METABOLIC EFFECTS OF ANTIPSYCHOTICS IN PREVIOUSLY ANTIPSYCHOTIC-NAïVE CHILDREN
John W. Newcomer, M.D.
Miller School of Medicine, University of Miami
The prevalence of overweight and obesity, insulin resistance and type 2 diabetes mellitus are increasing in children. Increased adiposity and reduced insulin sensitivity are major risk factors for future diabetes and cardiovascular disease, as well as other adverse health outcomes. Reductions in lifespan attributable to obesity impact younger individuals more than older individuals, with -for example- an expected 20-year reduction in life expectancy for severely

obese young adults. In children, diabetes and secondary comorbidities can progress more quickly than in adults, leading to earlier morbidity and mortality. Children and youth with mental illness are at increased cardiometabolic risk related in part to antipsychotic exposure, with limited understanding to date of drug specific effects on adiposity and insulin sensitivity during early treatment. This knowledge would be highly useful for evaluating the potential risks versus benefits of antipsychotic treatment in children. The NIMH-funded Metabolic Effects of Antipsychotics in Children (MEAC, PI Newcomer) study used state-of-the-art metabolic monitoring techniques to measure the effects of aripiprazole, olanzapine and risperidone on whole body and regional adiposity as well as whole body and tissue-specific insulin sensitivity, along with other measures glucose and lipid metabolism, in antipsychotic-naive youth ages 6-18 with target symptoms of aggression.

Antipsychotic-naive participants (N=125) aged 6-18 with clinically significant aggression and irritability (score of > 18 on Aberrant Child Behavior Checklist Irritability Subscale) and one or more DSM IV diagnosis indicating a disruptive behavior disorder were enrolled and randomized to 12 weeks of treatment with aripiprazole (mean dose +/- SD; 6.0 +/- 4.5 mg/day), olanzapine (6.3 +/- 3.2 mg/day) or risperidone (1.0 +/- 0.6 mg/day) following baseline assessments. Baseline and 12 week measures included body composition analysis with DEXA and MRI, as well as metabolic testing that included a single stage hyperinsulinemic-euglycemic glucose clamp with stable isotopomer tracing. Insulin sensitivity at adipose tissue was measured via the rate of appearance (Ra) of labeled glycerol; insulin sensitivity at liver was measured via rate of appearance (Ra) of labeled glucose; insulin sensitivity at muscle was measured via the rate of disappearance (Rd) of labeled glucose, all during a clamped, insulin-stimulated condition. ANCOVA analyses were performed to evaluate time x treatment group changes in DEXA total % fat, whole body insulin sensitivity, glycerol Ra, glucose Ra and glucose Rd during 12 weeks of antipsychotic treatment.

Significant worsening in body composition and insulin sensitivity was observed during the first 12 weeks of antipsychotic treatment in previously antipsychotic naive youth. Significant changes from baseline in DEXA total % fat were observed during 12 weeks of antipsychotic treatment (time x treatment group: $F[2,124]=8.47$, $p<0.0001$). Significant differences were observed in the pairwise comparisons between olanzapine and risperidone ($F[1,83]=11.34$, $p=0.001$) as well as between olanzapine and aripiprazole were observed ($F[1,79]=14.26$, $p<0.0001$). Significant changes from baseline were observed in whole body insulin sensitivity during 12 weeks of antipsychotic treatment (time x treatment group: $F[2,121]=3.32$, $p=0.04$). A significant difference was observed in the pairwise comparison between risperidone and aripiprazole ($F[1,84]=7.65$, $p=0.01$). Changes from baseline in Glycerol Ra were observed during 12 weeks of treatment (time x treatment group: $F[2,110]=2.64$, $p=0.08$); ANOVA (time x treatment group, $F[2,111]=4.26$, $p=0.02$). A significant pairwise comparison between olanzapine and aripiprazole was also observed ($F[1,69]=4.92$, $p=0.03$). A signficant reduction in hepatic insulin sensitivity was noted across pooled treatment groups (main effect of time: $F[1,112]=4.63$, $p=0.034$), with no significant difference across individual treatment groups (time x treatment group: $F[2,112]=1.47$, $p=0.23$). Significant changes from baseline in Glucose Rd were observed during 12 weeks of antipsychotic treatment (time x treatment group: $F[2,113]=3.87$, $p=0.024$). Significant pairwise comparisons were observed between olanzapine and risperidone ($F[1,75]=4.38$, $p=0.04$), as well as between risperidone and aripiprazole ($F[1,78]=6.05$, $p=0.02$). A significant relationship between change in DEXA percent fat and % change in Glycerol Ra was observed over 12 weeks of treatment ($F[1,113]=5.93$,

p=0.02). Antipsychotic treatment produced robust improvements in ABC irritability subscale and total scores, with no differences in the magnitude of beneficial effect observed across the randomized medication groups. Mean pooled group change in ABC irritability subscale score -16.6 (8.1) points, F[1,127]=538.36, p<0.0001; time x treatment group was not significant (F[2,125]=0.36, p=0.67).

Results from the MEAC study indicate rapidly detectable adverse effects of antipsychotic treatment on body composition (increased adiposity) and insulin sensitivity measured using gold standard methodology. Observed changes in DEXA total % fat are functionally significant, predicting reductions in the capacity of insulin to regulate triglyceride breakdown. The results suggest a key mechanism by which antipsychotic treatment can increase cardiometabolic risk during extended treatment. The results underline the importance of careful attention to the balance of potential risks and benefits during use of antipsychotic treatment in pediatric populations. Consistent with observations in adults, no clinically or statistically significant differences were observed on measurements of the psychiatric benefits of treatment across the individual medications tested. The results indicate the importance of careful medication selection to minimize risk while seeking the benefits of antipsychotic therapy.

Learning Objectives:
- Participants will understand the effect of antipsychotic treatment on adiposity.
- Participants will understand the effect of antipsychotic treatment on insulin sensitivity.

Literature References:
- Newcomer JW, Hennekens CH: Severe mental illness and risk of cardiovascular disease, JAMA, 2007, 298:1794-1796.
- Gohlke J, Dhurandhar E, Correll C, Morrato E, Newcomer J, Remington G, Nasrallah H, Crystal S, Nicol G, Allison: Recent advances in understanding and mitigating adipogenic and metabolic effects of antipsychotic drugs. Frontiers in Psychiatry, (2012); 3: 1-12.
- Yood MU, DeLorenze G, Quesenberry CP Jr, Oliveria SA, Tsai AL, Willey VJ, McQuade R, Newcomer JW, L'Italien G: The incidence of diabetes in atypical antipsychotic users differs according to agent – Results from a multisite epidemiologic study. Pharmacoepidemiol Drug Saf (2009); 18(9):791-799.
- Morrato EH, Nicol GE, Maahs D, Druss BG, Hartung DM, Valuck RJ Campagna E, Newcomer JW: Metabolic screening in children receiving antipsychotic drug treatment. Arch Pediat Adolesc Med (2010),164(4):344-351.

GENERAL DISCUSSION
Charles H. Hennekens, M.D.
Florida Atlantic University

PANEL
9:00 AM – 10:30 AM
PANEL OVERVIEW:
TACKLING THE BRAVE NEW WORLD OF MEDICINES DEVELOPMENT FOR AUTISM SPECTRUM DISORDERS
Robert H. Ring, Ph.D.[1], James McCracken, M.D.[2], Joseph P. Horrigan, M.D.[3], Linmarie Sikich, MD[4], Paul Wang, M.D.[5]

[1]*Autisim Speaks,* [2]*UCLA Neuropsychiatric Institute and Hospital,* [3]*Neuren Pharmaceuticals Limited, Auckland, New Zealand,* [4]*UNC-Chapel Hill,* [5]*Seaside Therapeutics, Inc.*

Autism Spectrum Disorder (ASD) is a disorder of brain development diagnosed behaviorally in the first years of life by the presence of a core triad of symptoms that feature difficulties with social interaction, verbal and nonverbal communication, and repetitive behaviors. Clinically, individuals with ASD are also beset with a heterogeneous array of comorbid psychiatric, neurological and somatic symptoms that, although not unique to ASD, can be a source of significant disability. Current epidemiological data from the Centers for Disease Control and Prevention estimate the identified prevalence of ASD to be 1 in 88 children, 1 in 54 boys, annually in the USA, making ASD as common as other familiar CNS conditions such as schizophrenia and Alzheimer's disease. In contrast to other CNS indications, however, only two drugs, risperidone and aripiprazole, have earned regulatory approval as treatments for individuals with ASD. The clinical target for these two drugs is actually a cluster of associated (non-core), comorbid symptoms referred to as irritability (eg irritability, self-injury, tantrums). Although these two drugs do deliver meaningful benefit to patients with ASD, there are currently no treatments approved to address the core symptoms of the disorder or any of the various associated psychiatric and neurological symptoms beyond irritability. When combined with the prevalence data, this represents a massive unmet medical need that is opening up significant opportunities for new medicines development. In response, a brave new world of new product development is now underway, and along with it has come many familiar and unprecedented challenges. The goal of this panel is to 1) define the opportunity drivers shaping the strategic direction of development activity in the space, 2) tackle and discuss the key challenges facing psychopharmacology discover and development, and 3) provide updates on several advanced clinical development programs in the space. Special attention will be placed on providing an overview of the changing diagnostic landscape in ASD emerging with the new DSM-V, along with a discussion on the current status of validation for outcome measures needed to pave a pathway to regulatory approval for a variety of different labels in ASD.

Learning Objectives:
- To introduce the challenges and opportunities inherent in the rapidly emerging field of pharmacotherapeutic development in autism and related neurodevelopmental disorders.
- To establish an awareness and understanding for the changes to how autism spectrum disorders will be diagnosed with new changes being made to the DSM-V.

INDIVIDUAL ABSTRACT:
A REVIEW OF HIGH QUALITY OUTCOME MEASURES FOR USE IN AUTISM SPECTRUM DISORDER (ASD) CLINICAL TRIALS

Joseph P. Horrigan, M.D.
Neuren Pharmaceuticals Limited, Auckland, New Zealand

In January 2011, Autism Speaks initiated a systematic review of outcome measures for potential use in autism spectrum disorder (ASD) clinical trials. The experts that engaged in the process of identification and vetting of potential measures came from academia, regulatory agencies, patient advocacy groups, and industry, and included the authors of several of the measures under review. The outcome measures were parsed into 3 groups, based on their capacity to assess social communication deficits, restricted/repetitive behaviors, and anxiety associated with ASDs. A face-to-face meeting was convened in 2012 to review the preliminary output of this process, and subsequently, the experts winnowed the possibilities in a serial manner to arrive at a consensus

hierarchical list of "appropriate", "appropriate with conditions", "potentially appropriate", "unproven" and "inappropriate" measures. Key considerations included the clinical relevance of the measures as well as their psychometric properties. This presentation will provide an update on the output of this endeavor, and will discuss some of the remaining unmet needs in terms of high quality outcome measures for use in ASD clinical trials.

Learning Objectives:
- At the end of this presentation, the participant will better understand the range of existing high quality outcome measures that are appropriate for use in ASD clinical trials
- At the end of this presentation, the participant will better understand the key areas of unmet need with regard to high quality outcome meaures for use in ASD clinical trials

Literature References:
- Aman M. et al. (2004), Outcome measures for clinical drug trials in autism. CNS Spectrums. 9(1):36-47.
- Ozonoff S et al. (2005), Evidence-Based Assessment of Autism Spectrum Disorders in Children and Adolescents. Joumal of Clinical Child and Adolescent Psychology 34(3):523-540

INDIVIDUAL ABSTRACT:
THE CHALLENGES FACING AN ACADEMIC INTERESTED IN THE DEVELOPMENT OF NOVEL TREATMENTS FOR AUTISM: MY EXPERIENCES WITH OXYTOCIN
Linmarie Sikich, M.D.
UNC-Chapel Hill

BACKGROUND: There is increasing information about genetic, environmental and neurodevelopmental factors that contribute to the pathophysiology of autism spectrum disorders (ASD). Many investigators seek to translate such information into novel human treatments for ASD. However, many academics have limited familiarity with all the FDA requirements for developing new drugs, particularly for the pediatric population. In addition, academics typically have access to very limited funding which may not support key elements of the drug development process.METHODS: Oxytocin has extensive animal and preclinical data supporting its key role in the salience of social relationships and social attention. It also has a long history of FDA approval for acute use in adult women based on its peripheral actions on the uterus and breasts. Recently, we have begun federally funded work to examine the impact of sustained oxytocin supplementation in children with ASD to enhance reciprocal social functioning. This presentation will describe the regulatory and design challenges that have been encountered thus far in the ACE SOARS network.RESULTS: In the course of implementing our funded Phase 2 trial, we have been confronted with multiple drug development issues. The first issue was related to demonstrating that intranasal administration of oxytocin reached the brain and interacted with targets that are involved in social behaviors. The second involved determining the pharmacokinetic profile of intranasal oxytocin in the brain, which is complicated by the limited relationship between serum and brain levels of oxytocin and oxytocin's ability to induce its own release. The third issue related to the absence of preclinical testing of the safety of oxytocin when given for sustained periods and when given to children. There are also unresolved issues related to the pharmacodynamics of oxytocin supplementation in order to determine appropriate dose ranges. Finally there have been a number of issues related to obtaining medication from international sources and formulating a more concentrated

preparation to optimize participant compliance and drug absorbtion. It was possible to budget for some of the required development steps, but many are outside the scope of typical clinical trials or may not be competitive with more innovative applications given the limited research funding currently available. Partnering with industry sponsors is also challenging given the off-patent status of oxytocin as well as public skepticism about the scientific integrity of academic researchers working closely with pharmaceutical companies.CONCLUSIONS: Academic researchers need to be aware of all the steps involved in drug development prior to undertaking translational research in humans. Support for essential preclinical studies is necessary to take full advantage of advances in our understanding of the pathophysiology of ASD. Otherwise, translational research is likely to be limited to agents whose pediatric safety has already been demonstrated or to that undertaken by pharmaceutical companies.

Learning Objectives:
- Attendees will be aware of potential pathways to move from animal models to human clinical trials.
- Attendees will be aware of potential challenges in developing novel treatments focused on neurodevelopmental disorders, with and without the support of a comprehensive industry sponsored development program.
- Attendees will be aware of the challenges related to imprecise outcome measures.

Literature References:
- Modi ME, Young LJ (2012). The oxytocin system in drug discovery for autism: animal models and novel therapeutic strategies. Horm Behav. 61(3): 340-350. doi: 10.1016/j.y.beh.2011.12.010
- Bailey GP, Marien D, (2011). The value of juvenile animal studies

INDIVIDUAL ABSTRACT:
STX209 (ARBACLOFEN) FOR FRAGILE X SYNDROME AND FOR ASD: FROM GENE TO ANIMAL MODELS TO PATIENTS
Paul Wang, M.D.
Seaside Therapeutics, Inc.
While the prevalence of ASD has soared in the last 2 decades, drug development efforts for ASD are rare. The lack of a neurobiological foundation on which to base drug development for ASD, and the lack of validated outcome measures in ASD, are two explanations for the lack of progress on this indication.

One approach to illuminating the pathophysiology of ASD is to examine the neurobiology of single gene disorders that are strongly associated with it. Fragile X syndrome (FXS) is the most common, known genetic etiology for ASD. Genetic and pharmacologic rescue experiments in animal models of FXS demonstrate that many of its neurobiological phenotypes, from abnormal dendritic morphology to seizure susceptibility, can be rescued by mGluR5 antagonists, and by GABA-B agonists as well. A second, and potentially complementary, hypothesis on the pathophysiology of FXS and of ASD is that they are related more generally to deficiencies in inhibitory neurotransmission. This hypothesis received striking support in optogenetic studies in mice, demonstrating that elevation of excitatory neurotransmission impairs social behavior, and that these impairments can be rescued by augmenting inhibitory transmission.

A Phase 2, placebo-controlled crossover trial has been completed in FXS, with STX209, a specific GABA-B agonist. On the primary endpoint (ABC-Irritability), drug effects were matched by placebo improvements. However, post-hoc analysis showed statistically significant

improvement on the ABC-Social Avoidance score, a newly-validated, FXS-specific scoring algorithm for the ABC. Additional post-hoc analyses were conducted in the subgroup with more severe social impairments. This subgroup showed significant improvement on multiple global measures and on the Vineland-Socialization scale, a gold standard functional measure. The most common adverse events (AE) on drug were headache and sedation (both 8%). There was 1 serious AE on drug (increased irritability).

A separate Phase 2, parallel group study was conducted with STX209 in 150 subjects with non-syndromic ASD. Again, improvements on the primary endpoint (ABC-Lethargy/Social Withdrawal) were similar on drug and placebo, but significant improvement was found on the CGI-S, and numerical improvement on the Vineland-Socialization scale. When the Vineland analysis was limited to subjects who were rated by the same clinician at baseline and end-of-treatment, as the protocol had required, the drug effect was stastically and clinically significant. The most common AE on drug was somnolence (9%). There was 1 serious AE on drug (suicidal ideation), and one similar case on placebo that was not declared serious. Additional trials are underway to translate the pre-clinical findings on STX209 to patients with syndromic and non-syndromic ASD, and to establish the best endpoints for demonstrating treatment effect in these patient groups.

Learning Objectives:
- Explain the rationale for GABA-B agonism in the treatment of ASD and of fragile X syndrome
- Describe the clinical trial data on the efficacy and safety of STX209 in treating ASD and fragile X syndrome

Literature References:
- Henderson, C., Wijetunge, L., Kinoshita, M. N., Shumway, M., Hammond, R. S., Postma, F. R., et al. (2012). Reversal of Disease-Related Pathologies in the Fragile X Mouse Model by Selective Activation of GABAB Receptors with Arbaclofen. Science translational medicine, 4(152), 152ra128
- Berry-Kravis, E. M., Hessl, D., Rathmell, B., Zarevics, P., Cherubini, M., Walton-Bowen, K., et al. (2012). Effects of STX209 (Arbaclofen) on Neurobehavioral Function in Children and Adults with Fragile X Syndrome: A Randomized, Controlled, Phase 2 Trial. Science translational medicine, 4(152), 152ra127

GENERAL DISCUSSION
James McCracken, M.D.
UCLA Neuropsychiatric Institute and Hospital

PANEL
10:45 AM – 12:15 PM
PANEL OVERVIEW:
NCCAM PANEL ON MIND ALTERING MICROORGANISMS: INSIGHTS ON NOVEL THERAPEUTIC CNS TARGETS
Emmeline Edwards, Ph.D.[1], Emeran Mayer, M.D., Ph.D.[2], Patricia Hibberd, M.D. Ph.D.[3], Patricia Hibberd, M.D. Ph.D.[3], Paul H. Patterson[4], James Versalovic, M.D., Ph.D.[5], Jens Walter, Ph.D.[6]
[1]Division of Extramural Research NCCAM, [2]Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, David Geffen School of Medicine at UCLA, [3]Harvard Medical School

and Massachusetts General Hospital, [4]California Institute of Technology, [5]Baylor College of Medicine and Texas Children's Hospital, [6]University of Nebraska - Lincoln

Bidirectional brain gut interactions are well established as an important mechanism in the regulation of gut function in health and disease, as well as in the generation of feeling states such as nausea, satiety, and abdominal pain. However, a role for the gut microbiota in these interactions has only been recently implicated. The brain can influence the intestinal microbiota indirectly via changes in motility, secretion and permeability, even though little is known about the influence of orocecal and colonic transit times on the composition of the microflora, except in extreme cases such as bacterial overgrowth. In addition, the nervous system can directly influence the intestinal microbiota via signaling molecules released from cells in the lamina propria (enteroendocrine cells, neurons, immune cells) into the gut lumen. Intestinal microbiota to host communication can occur via multiple signaling mechanisms, which include, but are not limited to toll- like (TLRs) and nod-like receptors (NLRs), via various G-protein coupled receptors on the luminal surface of gut epithelial cells, via direct stimulation of immune cells in the lamina propria when intestinal permeability is altered, and via long distance endocrine effects of microbiota produced metabolites. Enterochromaffin (EC) cells represent an important bidirectional transducer between the gut lumen and the nervous system. Vagal afferent innervation of enterochromaffin cells provides a direct pathway for neuronal signaling to the central nervous system which may play an important role in pain and immune modulation, background emotions and other homeostatic functions. Preclinical evidence is consistent with such vagally mediated influence of the intestinal microflora composition on affective behaviors. We recently studied the effect of regular intake of a probiotic consortium, including B. lactis on resting state and emotional stimulus provoked brain activity in healthy human subjects in a randomized controlled trial, using functional magnetic resonance imaging (fMRI). Regular intake of the probiotic was associated with alterations both in resting state activity and in the engagement of the primary interoceptive cortex in response to emotional stimuli. In summary, there is growing evidence for a role of intestinal microbiota in complex bidirectional brain gut interactions in health and disease. Dysregulation of these interactions may be involved in the pathophysiology of acute and chronic GI disease states, as well as in a variety of metabolic, cardiovascular and psychiatric disorders.

Learning Objectives:
- Provide evidence for a role of intestinal microbiota in complex bidirectional brain gut interactions in health and disease.
- To present data on the dysregulation of these interactions and their involvement in the pathophysiology of acute and chronic GI disease states, as well as in a variety of metabolic, cardiovascular and psychiatric disorders.

INDIVIDUAL ABSTRACT:
SMALL MOLECULE-MEDIATED MODULATION OF IMMUNITY AND NEUROBIOLOGY BY THE MICROBIOME
James Versalovic, M.D., Ph.D.
Baylor College of Medicine and Texas Children's Hospital
The human microbiome contains millions of microbial genes that encode enzymes and signaling proteins involved in numerous metabolic modules and pathways. These pathways result in de novo biosynthesis or luminal (body cavity) bioconversion of dietary components into small molecules and metabolites with diverse biological functions. Small molecules such as biogenic

amines and neurotransmitters that are produced by the intestinal microbiome may function locally to module mucosal immunity or remotely to impact systemic immunity, neuro:immune interactions, or neural signaling in remote body sites. This presentation will summarize the latest knowledge regarding bacterial species and genes responsible for the generation of small molecules with immunomodulatory and potential neuromodulatory effects. An enhanced understanding of the microbiome and its metabonome may facilitate the development of new pharmaceuticals for "psychopharmacology", and new medicinal compounds may originate from the microbiome itself. Primary or candidate human drug targets will also be highlighted during this presentation.

Learning Objectives:
- Attendees will be aware of potential pathways to move from animal models to human clinical trials.
- Attendees will be aware of potential challenges in developing novel treatments focused on neurodevelopmental disorders, with and without the support of a comprehensive industry sponsored development program.

Literature References:
- 15. Thomas CM, Hong T, van Pijkeren JP, Hemarajata P, Trinh DV, Hu W, Britton RA, Kalkum M, Versalovic J. Histamine derived from Probiotic Lactobacillus reuteri suppresses TNF via modulation of PKA and ERK signaling. PloS ONE 2012;7(2):e31951. [PMC3285189]
- 10. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: Mechanisms of intestinal immunomodulation and neuromodulation. Therapeutic Advances in Gastroenterology; 2012 September, 1-13. [PMC Journal – In Process]

INDIVIDUAL ABSTRACT:
MICROBIOTA-GUT-BRAIN COMMUNICATION: DOES IT REALLY PLAY A ROLE IN HUMANS?
Emeran Mayer, M.D., Ph.D.
Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, David Geffen School of Medicine at UCLA

Bidirectional brain gut interactions are well established as an important mechanism in the regulation of gut function in health and disease, as well as in the generation of feeling states such as nausea, satiety, and abdominal pain. However, a role for the gut microbiota in these interactions has only been recently implicated. The brain can influence the intestinal microbiota indirectly via changes in motility, secretion and permeability, even though little is known about the influence of orocecal and colonic transit times on the composition of the microflora, except in extreme cases such as bacterial overgrowth. In addition, the nervous system can directly influence the intestinal microbiota via signaling molecules released from cells in the lamina propria (enteroendocrine cells, neurons, immune cells) into the gut lumen. Intestinal microbiota to host communication can occur via multiple signaling mechanisms, which include, but are not limited to toll- like (TLRs) and nod-like receptors (NLRs), via various G-protein coupled receptors on the luminal surface of gut epithelial cells, via direct stimulation of immune cells in the lamina propria when intestinal permeability is altered, and via long distance endocrine effects of microbiota produced metabolites. Enterochromaffin (EC) cells represent an important bidirectional transducer between the gut lumen and the nervous system. Vagal afferent innervation of enterochromaffin cells provides a direct pathway for neuronal signaling to the

central nervous system which may play an important role in pain and immune modulation, background emotions and other homeostatic functions. Preclinical evidence is consistent with such vagally mediated influence of the intestinal microflora composition on affective behaviors. We recently studied the effect of regular intake of a probiotic consortium, including B. lactis on resting state and emotional stimulus provoked brain activity in healthy human subjects in a randomized controlled trial, using functional magnetic resonance imaging (fMRI). Regular intake of the probiotic was associated with alterations both in resting state activity and in the engagement of the primary interoceptive cortex in response to emotional stimuli. In summary, there is growing evidence for a role of intestinal microbiota in complex bidirectional brain gut interactions in health and disease. Dysregulation of these interactions may be involved in the pathophysiology of acute and chronic GI disease states, as well as in a variety of metabolic, cardiovascular and psychiatric disorders.

Learning Objectives:
- Recognize the challenges of drug development for major psychiatric conditions where there is as yet limited elaboration of underlying biology. In particular, recognize the value of robust translational research in support of rational drug development.
- Recognize the need for more advanced clinical trial methodology to enhance the probability of success in large, regulatory-intent Phase 3 clinical trials.

Literature References:
- Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA. Modulation of the human gut-brain axis after 4-week intervention with a probiotic fermented milk product. Gastroenterology 2012
- Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric. Nat Rev Gastroenterol Hepatol. 2009 May;6(5):306-14.

INDIVIDUAL ABSTRACT:
MICROBIOME MANIPULATION AS A THERAPY IN A MOUSE MODEL OF AN ENVIRONMENTAL RISK FACTOR FOR AUTISM
Paul H. Patterson
California Institute of Technology
While autism is a neurodevelopmental disorder characterized by language and social deficits, recent studies have highlighted striking dysregulation in the neural, peripheral, and enteric immune systems of autistic individuals. There are also reports that subsets of children with autism spectrum disorder (ASD) display gastrointestinal (GI) abnormalities, including increased intestinal permeability and altered composition of GI microbiota. To explore potential connections between GI problems and the brain and behavior, we use a mouse model of an ASD risk factor, maternal immune activation (MIA). We tested the efficacy of probiotic treatment in MIA offspring that display the cardinal ASD behaviors and neuropathology. Pregnant mice are injected with the viral mimic poly(I:C) or saline on E12.5. Offspring are fed the probiotic bacteria, *Bacteroides fragilis*, at weaning for one week. Young and adult offspring are assessed for (i) intestinal barrier integrity by measuring leakage of FITC-dextran through the intestinal epithelium and tight junction expression, (ii) GI inflammation by cytokine Luminex array and histology, (iii) serum metabolome profiles by GC-MS and LC-MS. MIA offspring display decreased intestinal barrier integrity and corresponding changes in levels of tight junction proteins. These symptoms are associated with altered expression of colon cytokines and changes

in serum metabolite levels. Postnatal *B. fragilis* treatment ameliorates these GI abnormalities, and normalizes certain serum metabolites and several ASD-related behaviors. These studies highlight the potential relevance of the gut-brain axis for ASD, where manipulation of the intestinal microbiome can influence GI physiology and behavioral performance. The results raise the possibility of testing a probiotic therapy in individuals with autism and co-morbid GI symptoms. Moreover, the altered serum metabolite profiles in the MIA mouse model raise the possibility of testing particular metabolites as candidate biomarkers for subsets of human ASD.

Learning Objectives:
- Attendees will be aware of potential pathways to move from animal models to human clinical trials.
- Attendees will be aware of potential challenges in developing novel treatments focused on neurodevelopmental disorders, with and without the support of a comprehensive industry sponsored development program.

Literature References:
- Malkova NV, Yu CZ, Hsiao EY, Moore MJ, Patterson PH (2012) Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. Brain Behav Immun 26:607-16.
- Patterson PH (2011) "Infectious Behavior: Brain-Immune Connections in Autism, Schizophrenia and Depression", MIT Press, Cambridge, MA, 162 pp.
- Patterson, PH (2011) Maternal infection and immune involvement in autism. *Trends Molec Med* 17:389-94.
  Brown AS, Patterson, PH (2011) "The Origins of Schizophrenia", Columbia University Press, New York, 448 pp.
  Hsiao EY, Patterson PH (2013) Immune-mediated models of autism spectrum disorder. *Autism-Open Access*, in press.

INDIVIDUAL ABSTRACT:
BACTERIAL MICROBIOTA-HOST INTERACTIONS PROMOTE METABOLIC INFLAMMATION AND OBESITY: IMPLICATIONS FOR THE CENTRAL NERVOUS SYSTEM AND THE BRAIN-GUT AXIS

Jens Walter, Ph.D.
University of Nebraska - Lincoln
Department of Food Science and Technology, University of Nebraska, Lincoln

Human biology can no longer concern itself only with human cells; mammals are complex assemblages of mammalian and microbial (mostly bacterial) cells organized into functional organs, tissues, and cellular communities. Proposed mechanisms by which the microbiota and their production of metabolites may contribute to nutritionally induced inflammation and metabolic-related dysfunctional states including obesity may occur through the induction of endotoxemia by lipopoysaccharide translocation, effects on lipolysis leading to increased fat depots, activation of immune-cells, and hepatic synthesis of triglycerides. The inflammatory tone associated with obesity contributes to the pathologies of obesity-related diseases, and is also likely to affect the Central Nervous System and the Brain-Gut axis. Understanding of the complex interplay between diet, the microbiome, and metabolic inflammation will aid in the design of non-invasive therapies such as improved next-generation probiotics and other targeted interventions towards host-microbe biologic networks. However, the development of such therapies has to be informed by ecological and evolutionary insight. The mechanisms by which

the microbial communities in the gut evolved symbiotically with the human host to optimize energy harvest from ancestral diets has to be taken into consideration when trying to understand the role of gut bacteria in metabolic diseases in modern societies. The development of therapies will further require an improved understanding, informed by ecological theory, of how microbiomes assemble and how communities can be successfully modified.

Learning Objectives:
- Attendees will be aware of potential pathways to move from animal models to human clinical trials.
- Attendees will be aware of potential challenges in developing novel treatments focused on neurodevelopmental disorders, with and without the support of a comprehensive industry sponsored development program.

Literature References:
- Tagliabue A, Elli M. The role of gut microbiota in human obesity: Recent findings and future perspectives. Nutr Metab Cardiovasc Dis. 2012 Nov 10. doi:pii: S0939-4753(12)00217-7. 10.1016/j.numecd.2012.09.002. [Epub ahead of print] PubMed PMID: 23149072.
- Hullar MA, Lampe JW. The gut microbiome and obesity. Nestle Nutr Inst Workshop Ser. 2012;73:67-79. doi: 10.1159/000341288. Epub 2012 Oct 29. PubMed PMID: 23128767.

GENERAL DISCUSSION
Patricia Hibberd, M.D., Ph.D.
Harvard Medical School and Massachusetts General Hospital

PANEL
10:45 AM – 12:15 PM
PANEL OVERVIEW:
NEUROSCIENCE VS SERENDIPITY IN PSYCHIATRIC DRUG DEVELOPMENT: A DEBATE
William Z. Potter, M.D., Ph.D.[1], David Michelson, M.D.[2], Donald F. Klein, M.D., DSc [3], Larry Ereshefsky, Pharm.D., B.C.P.P.[4], Ira Glick, M.D.[5]
[1]NIMH, [2]Merck Research Laboratories, [3]MYU Langone Medical Center, [4]PAREXEL International, [5]Department of Psychiatry & Behavioral Sciences Stanford University School of Medicine

A debate format is proposed followed by a period of questions/comments from the floor to address both at a conceptual and operational level approaches to novel psychiatric drug development that are often viewed as conflicting. The focus is on establishing that a particular unproven mechanism (e.g. CRF1 antagonism) does or does not have impact on any psychiatric condition. A "target validation" approach has been argued to provide a more rational means of avoiding endless ultimately non-productive and difficult to interpret studies as with 5HT1A partial to almost full agonists. Many clinical experts worry about Type 2 errors and would like to see any compound tested in as many types of psychiatric patients as possible. The panel of debater s could either argue that perceived differences in these approaches are mostly a matter of semantics or make explicit the extent to which there are real unresolved differences that can have us working at cross purposes. The chair (Bill Potter) would serve as debate moderator.

Five panelists would be included in order to have representation from five relevant "camps" : government, industry, academia, for profit trial centers and the hybrid academic/clinical trial network (such as the Alzheimer's Disease Clinical Study Group). Each panelist would have 8

minutes to present on the topics specified below following which each would have up to 5 minutes to comment on any of the other four presentations. The remaining time (estimated to be 15 minutes assuming a 90min slot) would be for open audience participation.

Suggested presentation titles for the panelists from the five constituencies are:

Industry: Go/No Go Decisions with Unproven Drug Mechanisms & the "Fast Fail" Model (David Michelson from Merck)

Government: Effects of Specific Mechanisms on Brain Circuits and related Behavioral Domains (according to RDoC) (Bruce Cuthbert or other NIMH presenter)

Academia: Conceptual and Practical Approaches for Optimizing Serendipity in Psychiatric Drug Development (Don Klein)

For Profit CRO/SMO Field: Optimal Approaches to Proof of Concept Studies Utilizing Existing Structures and SOPs (Larry Ereshevsky, Parexel)

Hybrid Academic Trial Networks: Leveraging Academic Focus to Assess Unproven Mechanisms or Drugs in Psychiatric Disorders (Ira Glick).

Learning Objectives:
- Awareness of neuroscience circuit based concepts in novel drug development
- Understanding pros and cons of narrow theory drive drug development vs wide exploratory testing in humans

INDIVIDUAL ABSTRACT:
DEBATE ON NEW DRUG DEVELOPMENT: A PERSPECTIVE FROM WITHIN INDUSTRY
David Michelson, M.D.
Merck Research Laboratories
The Drug Discovery and Development ProcessDavid Michelson, M.D.Merck Research Laboratories

The process of bringing new medications to patients within industry typically begins with the identification of a therapeutic target for which 1) there is convincing evidence of relevance to a disease process (validation), and 2) there is a means of modulating the target pharmacologically. This is followed by the effort to discover chemical structures that have the desired pharmacologic activity, and refinement of these structures to molecules with properties consistent with a useful drug, as well as supporting safety pharmacology studies and drug manufacture processes. Developing compounds that have the desirable properties to take into human studies is difficult and resource intensive, and programs are necessarily driven by expectations of efficacy in a specific indication. Molecules that fail to provide efficacy in their planned indication are sometimes investigated further for other disorders ('repurposed'), but the resource intensity and high failure rates of such efforts create a relatively high barrier to pursuit of exploratory studies in the absence of strong validation for new indications.

Learning Objectives:
- Attendees will understand key drivers that inform the design and conduct of new drug development programs
- Attendees will understand some of the competing imperatives that must be balanced in developing new drugs

Literature References:
- Frank R and Hargreaves R. Clinical Biomarkers in Drug Discovery and Development. Nature Reviews: Drug Discovery 2:566-80 2003

- Kaitin K. Deconstructing the Drug Development Process: The Face of New Innovation. Clin Pharm Ther 87:356-61 2012

INDIVIDUAL ABSTRACT:
THE ROLE OF CROS AND CLINICAL TRIALS NETWORKS IN DESIGNING AND IMPLEMENTING CLINICAL DEVELOPMENT PROGRAMS: BEYOND TRADITIONAL 'ARMS AND LEGS' EXPECTATIONS
Larry Ereshefsky, Pharm.D., B.C.P.P.
PAREXEL International

Ideally, a partnership of expertise should drive drug development (pharma, academia, and CRO) since each of these organizational entities have complementary strengths. The application of precision medicine and a rigorous pre-clinical to clinical translational approach aimed at improving the survival rate of CNS compounds entering Phase II have been proposed by pharma and by research societies. Phase I studies should demonstrate proof of CNS penetration, target engagement, and at least a positive effect on relevant symptoms and/or the 'movement' of an instructive biological measure. Within this early development paradigm there is a growing rationale for enrollment of patient populations as early as the single or multiple ascending dose study and to use adaptive designs to efficiently characterize drug effect on relevant biological measures. These complex and frequently multi-part (combination) studies incorporating many corroborative assessments/biomarkers are frequently best run in specialized research units with a track record of conducting similar studies in the past. Additionally proficiency in performing PD/behavioral assessments while under the pressure of tight timelines for study completion also drives site selection.A logical extension of this approach is to design and execute small, well conducted ('mini') proof of concept studies in a selected sub-population of 'responsive' patients to the pharmacological target. To achieve pilot study signal detection (one tailed) for drug vs. placebo, requires the use of either a single 'super-site' or a small number of trusted and highly trained sites. These networks of excellence are typically identified and (re)assessed for sustained performance by CROs or academic managed SMOs. An 'old' concept now being re-appraised is the creation of high throughput platforms which screen a series of drugs in a range of CNS patient indications, underscoring the need for CRO-like structures. Designing and conducting high complexity early drug development protocols, while orchestrating numerous vendors (analytical, cognitive, imaging, scales training) are tasks well suited to CRO structures. Especially as strategic partnerships with Pharma have grown, CROs are increasingly considered as academic like contributors to the science underpinning precision medicine trials.

Learning Objectives:
- Efficacy data comparing clozapine to other antipsychotics
- Reasons why clozapine is underutilized in practice

Literature References:
- Nations K, Bursi R, Dogterom P, Ereshefsky L, Gertsik L, Mant T, Schipper J. Maximum tolerated dose evaluation of the AMPA modulator ORG 26576 in Healthy Volunteers and Depressed Subjects: A summary and method analysis of Bridging Research in support of Phase II dose selection. Drugs R & D. 2012;12(3): 1-13
- Jinhe L, Llano D, Ellis T, LeBlond D, Bhatherna A, Jhee S, Ereshefsky L, Lenz R, Waring JF. The effect of human cerebrospinal fluid sampling frequency on AB level in clinical trials. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 2011;1552-5260. May 2011

INDIVIDUAL ABSTRACT:
DISCOVERY OF ALL NEW MAJOR CLASSES OF PSYCHIATRIC DRUGS OCCURRED THRU SERENDIPITY: THIS CEASED IN 1969, WHAT CAN WE INFER AND DO ABOUT IT?

Donald F. Klein, M.D., DSc
MYU Langone Medical Center

The striking fall off in new psychiatric drugs is exacerbated by the industry's retreat from this area. Two major questions are addressed, Is the fall off due to the change in medical and hospital practice in terms of managed care. Is the emphasis on drug targets premature and presumptuous given our ignorance of the pathophysiology of syndromes?

Learning Objectives:
- To be able to identify genes that predict differences in the pharmacokinetics of antipsychotics. .

Literature References:
- Klein DF The loss of serendipity in psychopharmacology. . JAMA. 2008 Mar 5;299(9):1063-5.
- Klein DF, Glick ID, Shader RI. Central nervous system drug development, basic, and clinical researchJ Clin Psychopharmacol. 2011 Oct;31(5):553-4.
- J Child Adolesc Psychopharmacol. 2007 Jun;17(3):284-7.
  Commentary by a clinical scientist in psychopharmacological research.

INDIVIDUAL ABSTRACT:
HYBRID ACADEMIC TRIAL NETWORKS: LEVERAGING ACADEMIC FOCUS TO ASSESS UNPROVEN MECHANISMS OR DRUGS IN PSYCHIATRIC DISORDERS

Ira Glick, M.D.
Department of Psychiatry & Behavioral Sciences Stanford University School of Medicine

This presentation will focus on leveraging academic settings to study mechanisms underlining psychiatric disorders. Advantages and disadvantages of academic sites compared to other settings for drug discovery will be discussed.

Learning Objectives:
- At the conclusion of this presentation participants will be aware of the advantages of using academic centers to help to develop new drugs.
- At the conclusion of this presentation participants will be aware of the disadvantages of using academic centers to help to develop new drugs.

Literature References:
- Klein D, Glick ID: The Crisis Caused by the Withdrawal of Industrial Development of Psychiatric Therapeutic Drugs. Neuropsychopharmacology (in submission)
- Glick ID, Correll C, et al: Mid and Long-term Antipsychotic Efficacy and Effectiveness of Medications for Schizophrenia. Journal of Clinical Psychiatry 2011; 72: 1616-1627

INDIVIDUAL ABSTRACT:
EFFECTS OF SPECIFIC MECHANISMS ON BRAIN CIRCUITS AND RELATED BEHAVIORAL DOMAINS

William Z. Potter, M.D., Ph.D.
NIMH

The NIMH is leading an initiative to develop, for research purposes, new ways of classifying mental disorders based on dimension of observable behavior and neurobiological measures. This includes a program to identify fundamental components that may span multiple disorders (e.g. affect regulation) and develop reliable and valid measures of these components to be included in clinical research and trials. The goal is to integrate genetic, neurobiological, behavioral, environmental, and experiential components so as to move us toward the goal of personalized medicine of neuropsychiatric disease. Current NIMH contrasts (e.g. FAST) offer opportunities for studying effects of drugs with specific molecular actions on brain circuit function as well as these dimensions of observable behavior which have been structured as Research Domain Criteria (RDoc). This neuroscience based approach to drug development promises to uncover effects of novel agents on the brain and behavior that cut across current diagnostic categories and can form the basis of a new dimensional approach to treating patients. Valid measures of these fundamental components for use in basic and clinical studies affect regulation) and tie them to reliable and valid measures of these fundamental components for use in basic and clinical studies.

Learning Objectives:
- Understand examples of how to track both brain circuit function and relate it to behaviors
- Learn status of current efforts to align circuit function with behavioral assays that can be deployed in studies of novel agents

Literature References:
- Insel et al, Am J Psych, 2010
- Meyer-Lindenberg and Weinberger, Nat. REv. Neuorsciene, 2007

GENERAL DISCUSSION
William Z. Potter, M.D., Ph.D.
NIMH

PANEL
10:45 AM – 12:15 PM
PANEL OVERVIEW:
PLACEBO ANALGESIA: PSYCHOLOGICAL, NEUROPHYSIOOLOGICAL AND NEUROBIOCHEMICAL ASPECTS
Luana Colloca, M.D., Ph.D[1], Jon-Kar Zubieta, M.D., Ph.D.[2], Lauren Y. Atlas[3]
[1]National Institutes of Health, National Institute of Mental Health and National Center of Complementary and Alternative Medicine, [2]University of Michigan, Psychiatry, Radiology, [3]New York University

Placebos and placebo effects have held an ambivalent place in medicine for at least two centuries. On the one hand, placebos are traditionally used as controls in clinical trials to correct for biases. On the other hand, neuroscientists have mounted evidence that placebo effects can actually influence perception, symptoms, and the response to active medications. In this Panel, Luana Colloca MD, PhD, Lauren Atlas PhD, and Jon-Kar Zubieta MD, PhD, will bring together three perspectives of placebo research including psychological mechanisms, underpinning neuroimaging pathways and molecular substrates of the placebo effect with a special emphasis on the predictability of placebo responsiveness.

Dr. Colloca will present placebo analgesia as a model to investigate how placebo responses are formed. Recent findings support that placebo analgesic effects can be induced by verbal instructions, conditioning and social observation, thus challenging some traditional

psychological perspectives posing that conditioning and expectations are the mechanisms inducing placebo effects. Moreover, Dr. Colloca will show how placebo responses can be elicited in clinical settings even if no placebo treatments are given, indicating which factors should be systematically taken into account to improve research methodology and identify potential predictors of placebo responses.

Dr. Atlas will show how placebo effects affect the human brain, and how the brain in turn shapes experience of pain under the administration of either placebos or active painkillers. Placebo effects influence the transfer of noxious inputs to brain, modulating nociception and pain evaluation in canonical pain-processing network (PPN) regions. Dr. Atlas will show how placebo effects interfere with objective brain responses to pain, even in the presence of strong analgesic treatments such as remifentanil. These effects are of invaluable importance when we assess the response to painkillers.

Dr. Zubieta will discuss molecular imaging approaches in understanding the neurobiology of placebo effects. Dr. Zubieta will show how the regional release of endogenous opioids and dopamine during placebo administration are associated with the formation of analgesic responses. Moreover, Dr. Zubieta will present recent findings showing that genetic factors, as well as personality traits can explain a substantial

proportion of the variance in placebo analgesic responses. These data emphasizes that placebo effects are related to specific neurobiological mechanisms and can be potentially predicted, of importance for patient stratification in clinical trials.

Learning Objectives:
- Upon completion of this session, attendees will be able to understand the most relevant psychological mechanisms inducing placebo analgesic effects, the brain patterns involved in the placebo analgesia, and the neurobiological nature of this phenomenon including the linkage between psychological traits and release of endogenous opioids.
- The integration of the voices of three researchers in the field with different expertise, will offer a unique opportunity to engage a broad audience including scientists with a basic, psychological and clinical background.

INDIVIDUAL ABSTRACT:
PLACEBO ANALGESIA AS A MODEL TO UNDERSTAND THE PLACEBO EFFECT
Luana Colloca, M.D., Ph.D
National Institutes of Health, National Institute of Mental Health and National Center of Complementary and Alternative Medicine
Dr. Colloca will present recent findings supporting that placebo analgesic effects can be induced by verbal instructions, conditioning and social observation, thus challenging some traditional psychological perspectives posing that conditioning and expectations are the mechanisms inducing placebo effects. The speaker will comment on data showing that the exposure to the experience of effectiveness elicited placebo analgesic responses that are present after four to seven days. Conversely, if a placebo is given after an ineffective procedure, the placebo effect is remarkably reduced, thus suggesting that prior successful, and unsuccessful experiences bias the outcome of a subsequent treatment. Placebo analgesic effects might also occur without a history of actual first-hand experience because observation and social learning may convey information that is necessary to build up expectation of benefit. The observation of a benefit in another person produced placebo responses that are similar in magnitude to those induced by directly experiencing the benefit through the conditioning procedure. These observations emphasize that

the contextual cues and the whole atmosphere around the subject contribute to induce expectation of benefit and thus, placebo analgesic responses. Interestingly, these effects can be triggered by cues that are not consciously perceived and conditioned placebo analgesic responses can be activated by cues operating outside of conscious awareness Moreover, Dr. Colloca will talk about the formation of placebo responses in clinical settings even if no placebo treatments are given, indicating which factors should be systematically taken in account to improve research methodology.

Learning Objectives:
- To unravel the psychobiological mechanisms undelying placebo effects.
- To understand the potential interaction between placebo and drug effects.

Literature References:
- Colloca L, Benedetti F. Placebo analgesia induced by social observational learning. Pain, 2009, 144:28-34. Comment in: Placebo analgesia: Widening the scope of measured influences. Pain 2009 Jul;144(1-2):5-6.
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INDIVIDUAL ABSTRACT:
EXPECTANCY EFFECTS DURING OPIOID ANALGESIA: INFLUENCES OF EXPECTATIONS ABOUT STIMULI AND EXPECTATIONS ABOUT TREATMENTS ON PAIN AND NEURAL RESPONSES

Lauren Y. Atlas
New York University

In this talk, I will present recent work examining the role of expectancy during opioid analgesia. It has long been believed that expectations enhance the effects of active pharmacological treatments. Though common brain regions are influenced by both placebo and opioid treatments, it is unknown whether knowledge of drug delivery influences pain-related brain responses during drug treatment. In two studies, we compared the effects of Open versus Hidden administration of remifentanil, a potent opiate analgesic, on brain and behavioral responses to noxious thermal stimulation. In Study 1, remifentanil was administered during fMRI and crossed with a manipulation of placebo expectancies (Open – Hidden drug delivery context). We assessed whether placebo enhanced drug effects on pain-evoked responses. In Study 2, we used a balanced placebo design to examine the relationship between opioid administration and placebo expectations. We also tested another kind of expectation: Expectations for high vs. low pain, driven by predictive cues presented immediately before painful stimuli.The results provide evidence for dissociable contributions of expectancy and opioid analgesia, both in behavioral reports and brain activity. Placebo and remifentanil each produced significant effects on pain in both studies. The effects were additive, suggesting that they produce separable effects on pain. In addition, in Study 2, we found additive effects of placebo and predictive cue-based expectancies on pain, and both effects were additive with drug effects. These results suggest that at least three factors can make separable contributions to pain modulation: opiate drug effects, placebo effects, and expectancies about noxious stimuli. Finally, I will present new network-based analyses that reveal that brain networks involved in pain, emotion, and cognition show distinct patterns of responses as a function of expectancy and opioid treatment.

Learning Objectives:

- To show that opioid analgesic treatments and information about drug delivery both reduce pain, but do so through dissociable neural mechanisms.
- To show that expectations about treatments and expectations about pain both modulate subjective pain reports.

Literature References:
- Atlas, L.Y., Whittington, R.A., Lindquist, M.A., Wielgosz, J., Sonty, N., & Wager, T.D. (2012). Dissociable influences of opiates and expectations on pain. The Journal of Neuroscience 32(23), 8053-8064.
- Atlas, L.Y., Bolger, N., Lindquist, M.A., and Wager, T.D. (2010). Brain mediators of predictive cue effects on perceived pain. The Journal of Neuroscience 30(39), 12964-12977.

INDIVIDUAL ABSTRACT:
MOLECULAR MECHANISMS OF PLACEBO EFFECTS
Jon-Kar Zubieta, M.D., Ph.D.
University of Michigan, Psychiatry, Radiology

In science, profound changes in paradigm have emerged when previously unexplained phenomena, typically disregarded as noise or measurement error, are explained by a new theoretical structure. That was the case for physics, when observations unaccounted for by classical mechanics led to the development of relativism, while the "noise" in relativity theory became the source of quantum physics. If a comparable phenomenon could be found in medicine, an unexplained source of variance, it would undoubtedly be the so-called "placebo effect", the elicitation of a change in biology as a consequence of inactive treatments. Substantial neurobiological placebo effects have been described in a number of pathologies, with initial reports and the larger number of mechanistic studies on the topic arising from the field of pain. A network of regions, including the rostral anterior cingulate (rACC), dorsolateral prefrontal (DLPFC), orbitofrontal (OFC) and insular (INS) cortex, nucleus accumbens (NAC), amygdala (AMY) and periacueductal gray (PAG) have been implicated in various studies using clinical or experimental pain models, with dopaminergic and endogenous opioid neurotransmission playing a prominent role. Some of these regions and neurotransmitter systems overlap with neurobiological placebo responses described in other pathologies, such as Parkinson Disease (dopamine -DA, NAC) and in one study in Major Depression (MDD) and in affective regulation in a healthy sample (rACC, OFC). Recent data from our group has shown that in MDD, DA through D2/3 receptors, and endogenous opioids activating μ-opioid receptors, neurotransmitter systems involved in analgesic placebo effects, are also implicated in the formation of placebo antidepressant effects. The latter is consistent with data showing that the endogenous opioid system and μ-opioid receptors are involved in regulating stress responses, mood and affective states, and the known involvement of DA in saliency and reward mechanisms. Placebo effects are also subject to substantial interindividual variability, some of which could be explained by individual subject characteristics (e.g., certain personality traits), which in our sample approximately accounted for one-fourth of the variance in placebo analgesia. Other factors that appear to contribute include common genetic variations with impact on placebo mechanisms (e.g., COMT, MOPR1). The integration of this information across domains (genetic, imaging, psychophysical) would help develop clinical trials with more specialized, in depth information as to the non-specific (e.g., placebo) and specific effects of treatment.

Learning Objectives:

- Understanding mechanisms underlying the formation of biological placebo effects
- Learning variables that are likely to contribute to placebo effects, such as traits, genetics, or neural function

Literature References:
- Scott DJ, Egnatuck CM, Wang H, Koeppe RA, Stohler CS, Zubieta JK. Opposite dopamine and opioid responses define placebo and nocebo effects. Arch Gen Psychiatry 65:220-231, 2008
- Zubieta JK, Stohler CC. Neurobiological mechanisms of placebo effects. NY Acad Sci 1156:198-210, 2009

GENERAL DISCUSSION
Jon-Kar Zubieta, M.D., Ph.D.
University of Michigan, Psychiatry, Radiology

PANEL
10:45 AM – 12:15 PM
PANEL OVERVIEW:
TOWARDS A BETTER UNDERSTANDING OF MEDICATION ADHERENCE IN PATIENTS WITH SERIOUS MENTAL ILLNESS (SMI)
Craig N. Karson, M.D.[1], Martha Sajatovic, M.D.[2], Dawn Velligan, Ph.D.[3], Stephen R. Marder, M.D.[4], Peter J. Weiden, M.D.[5]
[1]CNK Consultants, [2]Case Western Reserve University School of Medicine, [3]Department of Psychiatry, Univ. Texas Health Science Center, [4]Semel Institute at UCLA and VA Greater Los Angeles, [5]UIC Medical Center

Medication adherence remains a key issue in the success of treatment for patients with serious mental illness (SMI). Nonadherence to antipsychotic medication and symptom exacerbation substantially impact each other and both increase the risk of relapse. Nonadherence has been associated with increased hospitalizations and use of health care resources, while adherence has been related to symptom reduction, remission, and increased likelihood of achieving recovery. Many factors affect antipsychotic medication adherence and necessitate an understanding of the complex nature of adherence in order to develop successful adherence interventions. Establishing a pattern of adherence is particularly important for first-episode patients to reduce the cycle of increasingly poor adherence, relapse and poor outcomes experienced by many patients who are nonadherent following initial discharge from an inpatient setting. In clinical practice, defining and assessing adherence is usually not a straightforward process but is a necessary initial step in improving patient adherence to antipsychotic medications.

The first presentation in this panel will characterize medication adherence and discuss the use of long-acting injectable antipsychotic therapy in first-episode patients to better understand adherence early in the disease process in patients with SMI. Antipsychotic medication adherence will be further examined within clinical and vulnerable subpopulations such as those with bipolar disorder and homeless patients. The significant positive impact of adherence on medical resource utilization will be reviewed with respect to the use of long-acting injectable antipsychotics. Presentation of methodologies to assess, track, and improve adherence will discuss both low- and high-tech solutions to achieving clinical improvement in antipsychotic medication adherence. Finally, panel discussion will address the integration of these concepts to improve the overall care and outcomes for patients with SMI.

Learning Objectives:

- Understand the issues around adherence across the clinical spectrum of patients with SMI.
- Appreciate the impact of adherence on health care costs and patient outcomes.
- Learn about methodologies that can track and improve adherence. Integrate information presented on medication adherence in SMI to improve health care and outcomes for these patients.

INDIVIDUAL ABSTRACT:
UNDERSTANDING THE ROLE OF LONG-ACTING ANTIPSYCHOTIC MEDICATION IN RECENTLY DIAGNOSED, FIRST-EPISODE SCHIZOPHRENIA: INFORMATION TRUMPS ADHERENCE
Peter J. Weiden, M.D.
UIC Medical Center

Background: Most treatment guidelines reserve long-acting antipsychotic therapy for patients who have established patterns of recidivism. Using long-acting therapies earlier in the course of illness – shortly after a diagnosis of schizophrenia is established – offers the opportunity for preventing these outcomes in the first place. However, clinicians hesitate to recommend long-acting therapy early on; often because of a belief the recommendation will be rejected out-of-hand or the fear that introducing long-acting therapy may disrupt the therapeutic engagement process.

Methods: A prospective randomized controlled trial conducted between 12/2004 and 3/2007 in patients with "first-episode" DSM-IV schizophreniform, schizophrenia, or schizoaffective disorder treated in an urban public mental health service. Subjects were randomized at a 2:1 ratio to recommendation of long-acting injectable risperidone microspheres (RLAI) (n = 26) or continuation oral antipsychotic (ORAL) (n = 11), for up to 104 weeks. Primary outcomes were: (1) time until initial nonadherence (a medication gap of ≥14 days) and (2) medication attitudes assessed with the Rating of Medication Influences (ROMI) scale.

Results: Over 80% of patients stopped medication within 104 weeks. There was an early adherence benefit favoring RLAI acceptors at 12 weeks but no significant difference between RLAI and ORAL in the time to initial nonadherence during the overall study. Medication attitudes did not differ between groups. Treating clinicians missed over 75% of nonadherent gaps in "real time", creating an illusion that nonadherence was more likely to occur in LAI patients.

Conclusion: Most "first-episode" patients who engage in outpatient treatment will accept a long-acting recommendation. Refusers do so because they have already decided to stop medication. Acceptance of RLAI was associated with an initial adherence benefit that was not sustained over time. Recommendation of LAI does not adversely affect adherence attitudes in first-episode patients. The small size of the study and low power limits interpretation but the few patients who remained adherent into a second year were all receiving RLAI. Nonadherence was more easily detected among first-episode patients treated with LAI therapy than it was with oral antipsychotic.

Learning Objectives:
- Understand drivers of adherence and nonadherence among recently diagnosed "first-episode" schizophrenia patients.
- Review the acceptability and effectiveness of long-acting therapy in this population.
- Understand the role of adherence theory in better understanding the potential advantages and limitations of using long-acting antipsychotic earlier in the course of illness.

Literature References:
- Weiden PJ, Schooler NR, Weedon JC, Elmouchtari A, Sunakawa A, Goldfinger SM. A randomized controlled trial of long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. J Clin Psych. 2009; 70(10):1397-1406.
- Weiden PJ, Schooler NR, Weedon JC, Elmouchtari A, Sunakawa-McMillan A. Maintenance treatment with long-acting injectable risperidone in first-episode schizophrenia: a randomized effectiveness study. J Clin Psych. 2012;73(9):1224-33.

INDIVIDUAL ABSTRACT:
UNDERSTANDING ADHERENCE IN CLINICAL SUBPOPULATIONS OF PATIENTS WITH SERIOUS MENTAL ILLNESS (SMI)
Martha Sajatovic, M.D.
Case Western Reserve University School of Medicine

Poor adherence with medication treatment is common in chronic medical and psychiatric conditions. For some vulnerable clinical subpopulations emerging data suggest that targeted approaches that address an individual's reasons for adherence (and nonadherence) can improve outcomes. Among people with bipolar disorder estimates of nonadherence range between 20% to 55% and poor adherence is associated with negative clinical outcomes such as relapse, hospitalization, or even suicide. A variety of factors such as patient age, marital status, gender, educational level, symptoms, side effects of medications, and comorbid substance abuse, as well as environmental factors such as psychosocial support and access to care affect treatment adherence among individuals with bipolar disorder. Poor adherence occurs across the life-span for individuals with bipolar disorder. An analysis of adherence with antipsychotic medication among adults age 60 and older with bipolar disorder (N = 17,388) suggests that approximately 20% of individuals are nonadherent with medications while another 18.9% are partially adherent with medication. Customized approaches that address critical issues such as knowledge of the role of medication in mood relapse prevention and managing complex medication routines can improve adherence and bipolar symptoms. Similarly, among one of the most vulnerable psychiatric populations—homeless people with schizophrenia—a customized psychosocial approach paired with long-acting injectable antipsychotic medication can improve adherence and psychotic symptoms while reducing rates of homelessness. While there is no clear consensus on the best ways to improve treatment adherence among all individuals with serious mental illness, it appears that effective approaches need to address and incorporate the specific challenges that can impact adherence such as psychiatric diagnosis, clinical characteristics, and access to services.

Learning Objectives:
- Gain an increased awareness of issues that impact adherence in clinical subpopulations of patients with SMI.
- Understand how to approach development of adherence interventions in clinical subpopulations of patients with SMI.

Literature References:
- Berk L, Hallam KT, Colom F, Vieta E, Hasty M, Macneil C, Berk M.. Enhancing medication adherence in patients with bipolar disorder. Hum Psychopharmacol 2010;25:1-16.

- Gonzalez-Pinto A, Mosquera F, Alonso M, López P, Ramírez F, Vieta E, Baldessarini RJ. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disord 2006;8:618-24.

INDIVIDUAL ABSTRACT:
MEDICAL RESOURCE UTILIZATION IN PATIENTS TREATED WITH LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTICS
Craig N. Karson, M.D.
CNK Consultants

We have previously shown that initiation of LAIs may improve adherence to antipsychotic therapy and this concept is supported in the literature on treatment outcomes in schizophrenia. However, it is clinically useful to understand how treatment with LAIs impacts health care outcomes and use of health care resources during the course of illness in patients with schizophrenia. The objectives of these analyses were to examine the health care impact of initiating LAI antipsychotic treatment and to evaluate the impact of longer vs shorter duration LAI usage on health care outcomes and resources. Patients with schizophrenia ≥13 years of age and initiating treatment with LAI antipsychotics between 7/1/2005 and 6/30/2010 were identified from the Thomson Reuters MarketScan® Research Medicaid database. Annualized health care utilization and costs for preinitiation (baseline period; 6 months of continuous medical/prescription coverage prior to initiation) and postinitiation (variable follow-up period) of LAIs were determined and compared. The study population was also grouped into longer duration (≥180 days of supply) vs shorter duration (P<0.0001 for both comparisons) with an associated reduction of $6901 (*P*<0.0001) in all-cause annualized health care costs for patients initiating LAIs. Patients with longer duration LAI usage (604±432 days) were slightly younger, had less comorbidity, shorter length of all-cause and schizophrenia-related hospital stays, and longer time-to-first hospitalization for any cause or for schizophrenia relapse vs patients with shorter duration LAI usage (86±43 days). Overall, the hospitalization burden and costs of schizophrenia were reduced after patients initiated treatment with LAIs and the study indicates that longer duration of LAI use may improve treatment success. Results of the study may have clinical implications when discussing treatment options with patients with schizophrenia.

Learning Objectives:
- Understand possible implications of longer duration vs shorter duration treatment with LAIs in patients with schizophrenia.
- Understand possible implications of longer duration vs shorter duration treatment with LAIs in patients with schizophrenia.

Literature References:
- Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res. 2011;127:83-92.
- Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011;168:603-609.

INDIVIDUAL ABSTRACT:
DEVELOPING METHODOLOGIES FOR TRACKING AND IMPROVING ADHERENCE

Dawn Velligan, Ph.D.
Department of Psychiatry, Univ. Texas Health Science Center
Poor adherence to antipsychotic medication leads to symptom exacerbation and relapse, and derails the process of recovery. Approximately 50% of individuals are poorly adherent to oral antipsychotic medications. Expert consensus guidelines recommend regular assessments for adherence. Many methods are available to assess adherence including self-report, physician impression, caregiver report, pharmacy records, electronic monitoring, plasma or urine analysis, and the use of tracer substances. Many of these methods are difficult to utilize in clinical settings. All methods involve error. Studies have demonstrated that self-report vastly overestimates adherence and that providers are poor judges of the level of adherence. Pharmacy records can overestimate adherence in cases in which individuals pick up medications but do not take them and underestimate recent adherence in patients who have a stockpile of medication. Electronic monitoring data can contain errors when bottles are opened but no medication is taken and can lead to lost data if caps are not put back on bottles. Plasma and urine analysis and tracer substances are most accurate in the days immediately preceding measurement, but may not provide a good picture of adherence over longer periods of time. None of these methods establish how often pills are actually ingested. A novel method involves pills that contain a data chip that records ingestion. An alternative strategy is the use of a brief provider checklist that identifies individuals who are not receiving optimal benefit from current treatment and for whom long-acting therapies may be an option to consider. There are a number of interventions to address problem adherence. Cognitive Adaptation Training is a psychosocial treatment using environmental supports such as signs, alarms, checklists, and electronic pill containers to prompt and encourage adherence. Data suggest significant improvements in adherence and maintenance of effects for at least 6 months following active treatment. Cognitive behavior therapy focuses on understanding the individual's experiences with, and beliefs about, medication treatments, and works to help the individual move toward recovery goals. Motivational therapy identifies the stage of change in which an individual enters treatment and works to increase motivation for change through the use of techniques such as tailored reflection. Long-acting injectable antipsychotic medications can improve adherence and the identification of problem adherence and can help the prescriber to separate poor efficacy from poor adherence.

Learning Objectives:
- Describe the pros and cons of at least four methods for assessing adherence to oral medications.
- Describe evidence-supported treatments that can improve adherence to oral medication.

Literature References:
- Velligan D, Mintz J, Maples N, Li X, Gajewski S, Carr H, Sierra C. A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. Available at: http://schizophreniabulletin.oxfordjournals.org/cgi/reprint/sbs116?
- Velligan DI, Sajatovic M, Valenstein M, Riley WT, Safren S, Lewis-Fernandez R, Weiden P, Ogedegbe G, Jamison J. Methodological challenges in psychiatric treatment adherence research. Clin Schizophrenia Related Psychoses. 2010;4(1):74-91.

GENERAL DISCUSSION

Stephen R. Marder, M.D.
Semel Institute at UCLA and VA Greater Los Angeles

PLENARY SESSION
2:00 PM – 3:30 PM
NIH OPEN FORUM WITH LEADERSHIP OF NIMH, NIDA, AND NIAAA

INDIVIDUAL ABSTRACT:
HARNESSING PRECLINICAL STUDIES TO IDENTIFY NOVEL DRUG TARGETS FOR ALCOHOL DEPENDENCE
Antonio Noronha, Ph.D., NIAAA, NIH
The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is a strong supporter of basic and clinical research aimed at identifying effective medications for the treatment of alcoholism. Currently, there are four FDA approved medications for the treatment of alcoholism, each showing moderate efficacy. The modest efficacy of these medications is due to the heterogeneous nature of alcohol dependence where some individuals respond better to a particular medication compared to another. For this reason, basic, preclinical research that NIAAA supports continues to be actively engaged in finding novel drug targets that could be used for future medications development. To this end, the search for new drug targets is harnessing the power of genomics. For example, genome-wide gene expression studies are identifying networks of genes that are regulated by alcohol in the brain. This systems approach has the advantage identifying key brain signaling pathways that could be targeted for medications development. These studies are being conducted in various animal models of alcohol dependence as well as in human alcoholic brain obtained at autopsy. Important gene networks have been identified including: GABA signaling and neuroimmune signaling. Further, the tools for examining epigenetic changes after alcohol are also being applied to identify new drug targets. In this regard, histone deacetylases have been implicated in alcohol withdrawal and histone deacetylase inhibitors are effective in ameliorating some of the symptomlogy of alcohol withdrawal including anxiety. These novel drug targets should prove to be useful leads in clinical studies as we move from the bench to the bedside in ongoing translational efforts.

INDIVIDUAL ABSTRACT:
MEDICATIONS DEVELOPMENT AT NIDA
Phillip Skolnick, Ph.D., D.Sc. (hon.)
In this brief overview, I will highlight recent developments in preclinical and clinical research with the potential to significantly impact the treatment of substance use disorders (SUDs). A novel target identified during the past year holds promise as a source of novel, non-addictive analgesics. This target is a truncated, six-TM splice variant of the opiate receptor; novel drug-like molecules that interact with this site are potent analgesics but do not appear to either depress respiration or produce physical dependence, and have only a limited effect on GI transit (Majumdar, et al., J. Med. Chem. 55: 6352, 2012). Converging lines of evidence suggest that both dopamine D3 and D4 receptor antagonists would be effective pharmacotherapies to treat multiple SUDs. The lack of safe and well tolerated tools has precluded testing this hypothesis in the clinic. The recent demonstration that buspirone is a high affinity antagonist at D3 and D4 receptors is consistent with its ability to block cocaine self-administration in non-human primates and reinstatement (a model of relapse) to both cocaine and methamphetamine in rodents (Bergman, et al., Int. J. Neuropsychopharmacol. 16: 445, 2013; Newman, et al., Biochem. Pharmacol. 84:882, 2012). Based on these findings, the CTN (NCT01641159) initiated a relapse

prevention trial of buspirone in cocaine use disorder. Several NIDA-sponsored studies failed this year, including trials of vigabatrin to treat cocaine dependence and bupropion to treat methamphetamine dependence. Based in part on a NIDA funded study, Titan Pharmaceutical filed an NDA for an implantable form of buprenorphine, and an advisory committee meeting is scheduled for Q1 2013. Among the more promising biological approaches to treat SUDs is the development of a genetically modified butyrlcholinesterase, capable of hydrolyzing cocaine ~1000-fold more rapidly than the wild type enzyme. Consistent with findings in rodents and non-human primates, Phase I studies have demonstrated that parenteral administration of this enzyme rapidly degrades intravenously administered cocaine for at least a week. NIDA and Teva Pharmaceutical Industries, Ltd. have agreed to conduct (under a CRADA) a Phase II safety and efficacy study of TV-1380 (containing this engineered esterase) in the treatment of cocaine dependence.

INDIVIDUAL ABSTRACT:
NIMH UPDATE
Philip Wang, M.D., Dr.P.H.
This presentation will provide an overview of recent national issues involving mental health as well as research activities by NIMH to respond to these. Recent research findings that suggest opportunities to develop better diagnostic, treatment, and preventive interventions will also be covered.

PHARMA PIPELINE SESSION
3:45PM- 6:00PM

INDIVIDUAL ABSTRACT:
SAFETY, PHARMACOKINETIC AND POSITRON EMISSION TOMOGRAPHY EVALUATION OF SEROTONIN AND DOPAMINE TRANSPORTER OCCUPANCY FOLLOWING MULTIPLE-DOSE ADMINISTRATION OF THE TRIPLE MONOAMINE REUPTAKE INHIBITOR BMS-820836

Zubin Bhagwagar, M.D., DPhil MRCPsych[1], Lieuwe Appel, Ph.D.[2], Roger M. Lane, M.D., MPH[3], David Burt[4], Feng Luo, BMS[3], Robert Risinger, M.D.[5], Gunnar Antoni[6], Matthew Cahir, PharmD[7], Sanjay Keswani, MBBS BSc MRCP[8], Ming Zheng[9], Wendy Hayes, DO[10]
[1]Bristol-Myers Squibb and Yale University, [2]Uppsala Section for nuclear medicine and PET, Dept of Radiology, Oncology and Radiation, Uppsala University, [3]Bristol-Myers Squibb, [4]GlaxoSmithKline, [5]Alkermes, plc, [6]Depa of Medicinal Chemistry Uppsala University, [7]-, [8]Bristol Myers Squibb, [9]Bristol-Myers Squibb Co., [10]BMS

Objective: The novel triple monoamine reuptake inhibitor BMS-820836 selectively inhibits the reuptake of serotonin, norepinephrine, and dopamine implicated in the pathophysiology of major depressive disorder (MDD). The aim of the present study was to determine the safety and tolerability, pharmacokinetic (PK) profile, and SERT and DAT occupancy using positron emission tomography (PET) following multiple daily doses of BMS-820836 in healthy volunteers.

Methods: Fifty-seven healthy volunteers (49 male; 8 female) were assigned to one of the following eight dose groups: 0.1, 0.25, 0.5, 1, or 2 mg/day without titration (24 male subjects); 3 or 4 mg/day with titration (13 male subjects); 1 mg/day without titration (6 female subjects) or

placebo (12 male subjects; 2 female subjects). In each group, subjects received either BMS-820836 or placebo (3:1) as an oral daily dose for 14 days.

Forty-two of the male subjects (33 BMS-820836; 9 placebo) participated in the PET study. SERT investigations (n=12: 9 BMS-820836; 3 placebo) were conducted in the 0.1, 0.25, and 0.5 mg/day dose groups. DAT investigations (n=30: 24 BMS-820836; 6 placebo) were conducted in the 0.5, 1, 2, 3, and 4 mg/day dose groups. BMS-820836 occupancy at SERT was determined using [^{11}C]MADAM, and at DAT using [^{11}C]PE2I at 8 h post-dose (pd) on Day 10 and 24 h pd on Day 15. Blood samples were collected before and after each PET scan to determine the plasma concentrations of BMS-820836. Striatal SERT and DAT occupancies were estimated using a simplified reference tissue model[4] with cerebellum as reference region.

Serial blood samples were also collected on Days 1 and 14, and trough blood samples were collected pre-dose on Days 5, 8,10, and 12 to characterize the PK of BMS-820836 and its active metabolite BMS-821007.

Results: Oral daily doses of BMS-820836 were generally well tolerated by the healthy subjects. There were no serious adverse events (AEs). Thirty-seven subjects (86%) who received BMS-820836 and 11 subjects (78.6%) who received placebo had one or more AEs during the study. Most common AEs overall were headache, fatigue, decreased appetite, and dizziness. Three subjects (BMS-820836, n=2, male; placebo, n=1, female) discontinued treatment due to moderate AEs.

PK analyses showed that BMS-820836 had a median time to observed maximum concentration of 4.0–5.5 h and a mean apparent elimination half-life ranging from 44 to 74 h. BMS-820836 reached steady state by Day 10 following 0.1–2 mg daily, and Day 12 following 3 mg titration. The target average striatal SERT occupancy of approximately 80% was achieved after multiple doses of BMS-820836 0.5 mg at both 8 h and 24–27 h pd. A near-linear relationship between dose and average DAT occupancy was observed for BMS-820836 from 1 mg to 3 mg at both 8 h and 24–30 h pd (range 14%–35%).

Conclusion: Oral doses of BMS-820836 ranging from 0.1 mg to 4 mg were generally well tolerated by healthy subjects. The PK profile of BMS-820836 supports once daily administration. At doses of 0.5 mg/day, BMS-820836 demonstrated occupancy levels of SERT and DAT consistent with known pharmacodynamic effects of antidepressant agents. BMS-820836 is currently in Phase 2 clinical development for treatment of MDD.

Learning Objectives:
- Review the Phase 1 development of Triple Monoamine Reuptake Inhibitor BMS-820836
- Review the SERT and DAT occupancy profile of BMS-820836

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

Bernard L. Silverman, M.D.[1], John M. Kane, M.D.[2], Mark S. Todtenkopf, Ph.D.[1], Dan Deaver, Ph.D.[1], Elliot Ehrich, M.D.[3]
[1]Alkermes, Inc., [2]The Zucker Hillside Hospital, [3]Alkermes Inc

A number of antipsychotic medications are associated with weight gain and significant adverse metabolic effects.[1] Additionally, schizophrenia is associated with a high incidence of comorbid substance abuse. Both of these factors are obstacles in the treatment and management of many patients with schizophrenia thus limiting patient adherence to medication and adversely impacting treatment outcomes.[1,2] Therefore, a medication that is effective in treating symptoms

of schizophrenia with an improved safety and tolerability profile may be a useful addition to the therapeutic armamentarium.

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

ALKS 33, a novel opioid modulator, acts as an antagonist at μ opioid receptors, with mixed agonist/antagonist activity at κ and δ receptors. Nonclinical studies suggest that ALKS 33 may be useful in mitigating or preventing OLZ-induced weight gain. Using a standard rodent model, it was demonstrated that co-administration of ALKS 33 mitigated OLZ-induced weight gain, whereas naltrexone did not.[3] In a subsequent study using non-human primates to investigate OLZ-induced changes in weight gain or metabolic effects, ALKS 33 attenuated OLZ-induced weight gain and fat accretion following 28-days of repeat daily dosing.[4]

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

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

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

References:
- Lieberman J, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Eng J Med. 2005; 353:1209-1223.
- De Hert M, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011; 10: 52–77.
- Todtenkopf MS, Dean RL, Brunner MJ, Knopp M, Deaver DR. The Novel Opioid Receptor Modulator RDC-0313 (ALKS 33) Reduces Olanzapine-Induced Weight Gain and Adipose Accretion in a Novel Nonhuman Primate Model of Antipsychotic-Related Weight Changes. ACNP 2011: Hot Topics and poster presentation, III-206.

- Todtenkopf MS, O'Neill KS, Kelly SM, Richie KA, Dean RL, Eyerman, DE, Deaver DR. RDC-0313 (ALKS 33), a Novel Opioid Receptor Modulator, Reduces Olanzapine-Induced Weight Gain in Female Rats. ACNP 2010: III-81.

INDIVIDUAL ABSTRACT:
PH 10 MAY BE A NEW RAPIDLY ACTING INTRANASALLY ADMINISTERED ANTIDEPRESSANT

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Purpose: There is a well-recognized need for more rapidly acting antidepressants. A novel class of compounds called pherines, which are intranasally administered neurosteroids, may have rapid and potent effects on major psychiatric syndromes. Positive placebo controlled results from PH94B in social anxiety disorder were presented at NCDEU in 2011. Here we present preliminary promising placebo controlled trial data on PH 10 in patients with major depression (MDD).

Introduction: PH 10 is a pherine, a small molecule that specifically engages peripheral chemoreceptors in the nasal passages, and triggers neural impulses that modulate the function of the limbic system, amygdale, hypothalmus, anterior cingulate gyrus and frontal cortex. After demonstrating safety in animals and normal human volunteers, a placebo controlled trial of PH 10 was initiated in patients with MDD.

Methodology: Thirty patients with MDD and a HAM-D -17 score of ≥ 17 were randomized to receive intranasally low dose PH10 (3200 ng/day), high dose PH10 (6400 ng/day) or placebo for 8 weeks. The primary outcome measure was the endpoint HAM-D score. Secondary outcome measures included changes in HAM-D scores during the 8 weeks of treatment, and CGI, and Q-LES-Q-SF.

Results: Results of the ANCOVA for group differences in HAMD scores (baseline HAMD as covariate) indicated a trend toward adjusted group differences at endpoint ($F(2,26) = 2.95$, $p = 0.070$). Exploratory pairwise comparisons for the least squares-adjusted group means indicated a trend toward difference between the placebo (mean = 10.36) and high dose group (mean = 6.15) at $t(18) = 2.23$, $p = 0.085$. The low dose adjusted mean (6.60) was not statistically different from that of other groups.

Further exploration showed an effect size (Cohen's d) of 1.13 for the low dose group and 0.77 for the high dose group when compared to the placebo group at endpoint. Rapid antidepressant benefit was also seen, with the low dose group showing an effect size of 1.05 and the high dose group 0.75 in comparison to placebo after one week of treatment.

Response ($\geq 50\%$ improvement on HamD) and remission (HamD ≤ 7) rates at endpoint were, respectively, 80% and 60% for low dose, 90% and 80% for high dose, and 60% and 20% for placebo. High-dose exceeded placebo in remission rate, ($z = 3.35$, $p = 0.023$), with low dose and placebo not statistically different ($z = 2.00$, $p = 0.170$) and no difference between the high and low dose ($z = 1.00$, $p = 0.628$). Group response rates were not statistically different. Comparisons on GGI and QLES Q at endpoint were not significant.

Side effects included increased appetite, day time sleepiness, nasal dryness and headache. Weight gain did not differ among groups.

Discusssion: These very preliminary results suggest Ph10 may be a novel, rapidly acting, potent and well tolerated antidepressant. Further trials are clearly indicated.

Learning Objectives:

- 1. To familiarize attendees with the antidepressant efficacy of PH10
- 2. To explore the rapidity of onset of antidepressant effects of PH10

INDIVIDUAL ABSTRACT:
DOSE RESPONSE ANALYSIS OF LISDEXAMFETAMINE DIMESYLATE FOR TREATMENT OF BINGE EATING DISORDER

Susan McElroy, M.D.[1], James Reynolds, M.S. [2], Joseph Gao, Ph.D.[3], Maria Gasior, M.D., Ph.D.[2]
[1]LIndner Center of HOPE, The University of Cincinnati College of Medicine, [2]Shire, [3]Shire Development LLC

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

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

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

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

Learning Objectives:

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

INDIVIDUAL ABSTRACT:
SUVOREXANT: OREXIN RECEPTOR ANTAGONISM AND INSOMNIA
David Michelson, M.D.
Merck Research Laboratories
Suvorexant is a novel orexin receptor antagonist current under review by the US FDA as a potential new agent for the treatment of insomnia. The phase 3 program was recently completed, and includes 3 large studies assessing the safety and efficacy of suvorexant. The results of these studies provide evidence supporting the efficacy of suvorexant for the treatment of insomnia, including disturbances of sleep onset as with well sleep maintenance, with favorable safety and tolerability profile. The suvorexant development program and results will be discussed during this presentation.
Learning Objectives:
- To understand the role of orexin receptor antagonists in the treatment of primary insomnia
- To understand the efficacy, safety and tolerability of suvorexant

INDIVIDUAL ABSTRACT:
PHARMACOLOGY, SAFETY AND EFFICACY IN MAJOR DEPRESSIVE DISORDER OF CX-157, A REVERSIBLE INHIBITOR OF MONOAMINE OXIDASE A
Daniel J. Burch, M.D.
PPDi
CX-157 is a reversible inhibitor of monoamine oxidase A is being developed for major depression. PET imaging studies in humans have confirmed target engagement and reversible pharmacology. PK/PD relationships support a 125mg bid dosing schedule. The 125 mg bid formulation was tested in a tyramine challenge study and demonstrated no cardiovascular effect at tyramine doses up to 80mg. A large well-controlled safety and efficacy study in which 360 subjects with major depression that had responded unsatisfactorily to previous treatment were randomized evenly to active and matching placebo demonstrated CX157 was safe and well-tolerated, but did not meet it's primary efficacy endpoint. A post hoc band pass analysis suggested evidence of clinical efficacy.
Learning Objectives:
- Understand considerations for developing a novel anti-depressant
- Understand factors contributing to the assay sensitivity of an anti-depressant safety and efficacy trial

INDIVIDUAL ABSTRACT:
A RANDOMIZED, DOUBLE-BLIND, STUDY OF VORTIOXETINE VERSUS AGOMELATINE IN ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD) SWITCHED AFTER INADEQUATE RESPONSE TO SSRI OR SNRI TREATMENT
Marianne Dragheim, M.D., Rebecca Z. Nielsen, MSc.
H. Lundbeck A/S

Background: The investigational antidepressant vortioxetine (Lu AA21004) is a multimodal 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter [1]. Data from randomized trials comparing treatment strategies in patients who were unresponsive to first-line antidepressant treatment are limited. In the large open-label STAR*D study in which patients received treatment with citalopram (level 1) and non-responders were randomly switched to a second treatment (level 2), the mean remission rate after 12-14 weeks was 30.6% [2].

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

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

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

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

[1] Bang-Andersen B, et al. J Med Chem 2011;54:3206-21.
[2] Rush AJ, et al. Am J Psychiatry 2006;163:1905-17.

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

INDIVIDUAL ABSTRACT:
TREATMENT OF DEPRESSION WITH ONABOTULINUMTOXINA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL

Eric Finzi, M.D., Ph.D.[1], Norman Rosenthal, M.D.[2]
[1]Chevy Chase Cosmetic Center, [2]Georgetown University School of Medicine

Existing treatments for major depression are ineffective, or only partially effective for many patients. Developing novel antidepressant strategies would have a major impact on patient care. Converging lines of evidence suggest a role for facial expressions in the pathophysiology and treatment of mood disorders.

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

In the OBA group, the effortful frown score at the 6 week visit was significantly correlated with MADRS response ($p < 0.02$, Spearman correlation coefficient), and with MADRS remission ($p < 0.03$, Spearman correlation coefficient) ; lower 6 week frown scores correlated with lower MADRS scores, and higher remission rates.This is the first randomized, double blind, placebo-controlled clinical trial to show that a single treatment of the glabellar region with OBA induces a strong and sustained alleviation of symptoms in a broadly defined group of people with major depression, including patients not regarded as treatment resistant. Our trial is the first to show statistical significance for remission of depression after a single treatment with OBA to the glabellar frown muscles. Trial Registration: clinicaltrials.gov Identifier: NCT01556971

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

INDIVIDUAL ABSTRACT:
GEPIRONE-ER: EFFECTIVE TREATMENT OF MAJOR DEPRESSION AND ACCOMPANYING SEXUAL DYSFUNCTION
Louis C. Smith, Ph.D., Louis F. Fabre, Jr., M.D. Ph.D.
Fabre Kramer Pharmaceuticals, Inc.
Specific purpose: to improve treatment outcome in major depression.
Background: Current treatments of Major Depression do not take into consideration the 80% of depressed subjects who have sexual dysfunction at baseline. Only 30% of treated depressed

subjects attain remission. Current treatments of depression do not improve sexual function. In fact, the Serotonin Reuptake Inhibitors (SSRIs) and the Serotonin Nor-epinephrine Reuptake Inhibitors (SNRIs) further compromise sexual function. There have been no approved pharmacologic treatments or combinations of treatments that will improve both depression and sexual dysfunction. Gepirone-ER, a 5-HT$_{1A}$ agonist may achieve successful treatment of Major Depression and Sexual Dysfunction.

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

Results: Two studies of Gepirone-ER in Major Depression subjects showed statistically significant antidepressant activity as measured by the HAMD-17 change from baseline. Study 134001 HAMD-17 effect size -2.47, p=0.013, and FKGBE007 effect size -2.45, p=0.018. These two studies did not have SSRI comparators and only 134001 had sexual function measurements. DISF results for 134001 gepirone-ER treated vs. placebo men and women combined are DISF total score effect size +6.1, p=0.017, and DISF desire domain effect size +2.3, p=0.043.
Four studies pooled show positive effects for gepirone-ER on sexual function. DISF change from baseline total scores were gepirone-ER 5.33 (p=0.04 better than placebo), fluoxetine (only 2 studies) -4.25 (p=0.01 worse than placebo) and placebo 1.73.

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

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

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

Marc Cantillon, M.D.[1], Mike Li, MS[2], Sarath Kanekal, Ph.D., DABT, RAC[1], Robert M.J. Ings, Ph.D.[3], Grace Tung, RAC[4], Laxminarayan Bhat[5]
[1]Reviva Pharmaceuticals, [2]Reviva, [3]RMI-Pharmacokinetics, [4]Grace Tung Consulting, [5]Reviva Pharmaceuticals Inc

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

Methods: The REFRESH Phase 2 trial was to assess the safety & efficacy of RP5063 (15mg, 30mg and 50mg) administered to subjects with an acute exacerbation of schizophrenia or schizoaffective disorder, as measured by change from baseline to Day 28 on the Positive and Negative Syndrome Scale (PANSS) total score.

Each subject participated in the study for up to 7 weeks. The study comprised of a screening period (Day minus 6 to Day 0), baseline (Day 1 pre-dose) and fixed dose treatment period (Day 1 to Day 28) and follow-up visit for re-stabilization after 1 week of the last dose of study treatment (Day 35±2. Subjects between 18 and 65 years with a clinical diagnosis of acute exacerbation of schizophrenia or schizoaffective disorder (at least one year prior to screening) according to DSM-IV-TR criteria were entered. Screening score for the acute psychosis on the BPRS of >36 and BPRS psychosis cluster a minimum score of 4 or higher on at least two of the four items: suspiciousness, conceptual disorganization, hallucinatory behavior, and/or unusual thought content

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

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

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

INDIVIDUAL ABSTRACT:
BROAD THERAPEUTIC POTENTIAL FOR ITI-007 AND IC200131

Kimberly Vanover, Ph.D.
Intra-Cellular Therapies, Inc.

Background: ITI-007 is an investigational new drug that represents a unique approach to serotonergic, dopaminergic, and glutamateric modulation, with differing pharmacology depending on dose. *In vitro*, ITI-007 is a potent serotonin 5-HT2A receptor antagonist with approximately 60-fold separation between 5-HT2A and other neuropharmacological targets. As its concentration is increased, ITI-007 exhibits cell-type specific modulation of dopamine D2 receptors. *In vivo*, ITI-007 acts as a pre-synaptic partial agonist and post-synaptic antagonist

with mesolimbic/mesocortical selectivity. Along with cell-type specific dopaminergic modulation, higher concentrations of ITI-007 increases phosphorylation of mesolimbic GluN2B subunits of N-methyl-D-aspartate (NMDA) channels, consistent with enhancement of glutamatergic neurotransmission, and inhibits serotonin reuptake. Together, these data suggest different therapeutic utility at low doses of ITI-007 compared to higher doses. Adding to this unique profile, ITI-007 is metabolized into IC200131, a serotonin-2A (5-HT2A) receptor antagonist and inhibitor of serotonin reuptake with roughly equal potency at each of these two targets. Interestingly, IC200131 is back-converted into ITI-007. The pharmacology of IC200131 was explored further *in vivo* in preclinical models.

Methods: Orally administered IC200131 was evaluated for its ability to reduce head-twitch behavior induced by a 5-HT2A receptor agonist (quipazine) and to reduce amphetamine-induced hyperactivity in rodents.

Results: In rodents, IC200131 reduced quipazine-induced head-twitches and inhibited amphetamine-induced locomotor activity, consistent with 5-HT2A receptor antagonism and antipsychotic efficacy, respectively.

Discussion: The pharmacological activity of IC200131 and back-conversion of IC200131 into ITI-007 extends the effective half-life and enhances the therapeutic potential of ITI-007. Moreover, IC200131 was selected as a development candidate as a treatment for mood symptoms associated with neuropsychiatric and neurological disorders. It is anticipated that the 5-HT2A receptor antagonist properties of IC200131 will lead to improved sleep, reduced aggression and better impulse control. Serotonin reuptake inhibition induced by IC200131 will reduce depression and other dysthymic symptoms, while its 5-HT2A receptor antagonism will enhance antidepressant efficacy and reduce sexual side effects. Through its conversion to ITI-007, IC200131 gains dopaminergic protein phosphorylation modulator activity and glutamatergic protein phosphorylation modulation. The combined actions of IC200131 and ITI-007 present a novel pharmacologic profile that may have broad utility in treating neuropsychiatric and related disorders. ITI-007 is in Phase 2 clinical development for acute and residual schizophrenia and IC200131 is currently in preclinical development.

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

INDIVIDUAL ABSTRACT:
EVP-6124, AN ALPHA-7 NICOTINIC PARTIAL AGONIST, PRODUCES POSITIVE EFFECTS ON COGNITION, AND CLINICAL FUNCTION IN PATIENTS WITH CHRONIC SCHIZOPHRENIA ON STABLE ANTIPSYCHOTIC THERAPY
Ilise Lombardo, M.D.
EnVivo Pharmaceuticals
It is well recognized that patients with schizophrenia have persistent cognitive deficits despite treatment with antipsychotics. Alpha-7 nicotinic acetylcholine receptor agonists (N-A7A) are of interest as potential procognitive therapy. These receptors may be linked to various domains of cognition, including attention and long term and working memory.EVP-6124 is a novel, potent, and selective N-A7A. Nine clinical studies with EVP-6124 have been completed in 561 unique

subjects (403 received EVP-6124, 158 received placebo). EVP-6124 was safe and well-tolerated and exhibited linear kinetics with a long half-life (>60 hours) suitable for once daily dosing.
Methods: A Phase 2b study in stable subjects with schizophrenia (n=319) receiving atypical antipsychotics has been completed. The study assessed the safety and efficacy of two doses of EVP-6124 (0.3 and 1 mg) versus placebo. Efficacy was evaluated by the Overall Cognition Index (OCI) from the CogState testing battery and Trails 2 and 4 of the Neuropsychological Test Battery (NTB) (all subjects), the MATRICS Consensus Cognitive Battery (MCCB) (US subjects only), the Schizophrenia Cognition Rating Scale (SCoRS) and the Positive and Negative Syndrome Scale (PANSS). Statistical results, as defined in the protocol, were considered significant at $P < 0.10$ (one-sided tests).
Results: Stable subjects with schizophrenia, both smokers and non-smokers, were treated with placebo (n=106), 0.3 mg (n=107) or 1 mg (n=106) of EVP-6124 for a total of 84 days.
The drug was well tolerated with no clinically significant findings with respect to ECGs, vital signs, hematology and serum chemistry or suicidal ideation and behavior. A total of 192 treatment-emergent adverse events (TEAEs) were reported in 101 (31.9%) subjects, including 25 (23.4%) subjects in the 0.3 mg group, 35 (33.3%) subjects in the 1 mg group, and 41 (39%) subjects in the placebo group. The most commonly reported TEAEs were headache (3.8%), nausea (3.2%) and nasopharyngitis (2.5%). The incidence of serious adverse events was similar among the three dosing groups; none were judged related to drug.
The OCI plus Trails 2 and 4 suggested that 0.3 mg of EVP-6124 compared to placebo, was associated with improvement in general cognitive function ($P = 0.034$) and that this improvement was due mainly to the beneficial effects of the drug on visual learning, visual attention, and social cognition. This positive effect on the OCI was supported by a strong positive trend (NS) for improved cognition on the MCCB Battery which was performed only in the US (n=166). For the 1 mg group, the mean change from baseline at day 84 in the overall Composite T-score and the associated percentile change were higher than for the 0.3 mg group and placebo.
Significant effects in clinical function were also seen with EVP-6124 as measured by the SCoRS Interviewer Rating of clinical function over all visits for the 1 dose group compared to the placebo ($P = 0.065$).
Discussion: In this study, EVP-6124 treatment of subjects with schizophrenia resulted in improved cognition and clinical function. EVP-6124 was well tolerated in this population. These data support the continued investigation of EVP-6124 in larger confirmatory trials which are currently ongoing.
Learning Objectives:
- Investigation of procognitive effects of a novel agent in patients with schizophrenia
- Measures of cognitive function and potential treatment effect in a clinical trial of subjects with schizophrenia

Wednesday, May 29, 2013
PLENARY SESSION
8:30 AM – 10:00 AM

PLENARY SESSION OVERVIEW:
CAN WE AFFORD TO CONDUCT CLINICAL TRIALS WITHOUT MONITORING ADHERENCE?

Raye Z. Litten, III, Ph.D.[1]
[1]NIAAA

When monitored by pill count, medication adherence in randomized controlled trials is generally >90%. However, dramatically lower rates have been reported by monitoring drug (and/or drug metabolite) levels, rather than pill count, as an adherence measure. Low rates of adherence have long been recognized as adversely affecting patient outcomes, but this problem has not been adequately addressed in the conduct of clinical trials. There are multiple examples of low medication adherence in neuropsychiatric drug trials that can lead to Type II errors. Incorporation of riboflavin into clinical trial material has been used as an adherence marker, but is far from ideal. Multiple emerging technologies are now available to improve (e.g. behavioral modification and information technology approaches) and/or more precisely monitor (e.g. 'chip in a pill' technology) adherence. Moreover, the ability to accurately monitor medication adherence and stratify data based on this information may ultimately impact the drug approval process.

INDIVIDUAL ABSTRACT:
IS UNDERSTANDING MEDICATION ADHERNECE THE CORNERSTONE OF A SUCESSFUL CLINICAL TRIAL?

Phillip Skolnick, PhD, D.Sc. (hon.)

The "gold standard" for measuring medication adherence in clinical trials is pill count. When monitored by pill count, adherence is generally reported as >90%. However, in studies where adherence is monitored by measuring drug (and/or metabolite) levels at periodic intervals, these rates are consistently and dramatically lower. In this presentation, I will describe studies that illustrate how low rates of medication adherence preclude rigorous hypothesis testing and may contribute to the high failure rate of neuropsychiatric drugs at the proof-of-concept stage and beyond.

INDIVIDUAL ABSTRACT:
CAN WE AFFORD TO CONDUCT CLINICAL TRIALS WITHOUT MONITORING ADHERENCE?

Aidan Hampson, Ph.D.

In all pharmacotherapeutic clinical trials, whether aimed at cardiovascular or psychiatric indications, there is a ghost in the machine; 'Adherence'- did the subjects take the medication as prescribed? This question is important to the trial sponsor, but critical to patients who would have had access to a new efficacious medication if a trial failure had not stopped further development. Even worse, if a medication is approved despite poor adherence in the trials, the minimum toxic dose might appear higher than in reality. Post marketing, this can result in patients experiencing toxic side effects when adhering to recommended dosages. Unfortunately, assessing true compliance in a trial is difficult, monitored medication ingestion is very labor intensive for subjects and clinical staff and so is usually only suitable for small trials. This talk will briefly discuss the current 'standard' procedures in use to monitor medication compliance, as well ways in which NIDA is trying to sponsor the development of new improved tools designed to aid trial clinicians to wrestle the adherence 'ghost'.

INDIVIDUAL ABSTRACT:
BEHAVIORAL AND TECHNOLOGICAL STRATEGIES TO ENHANCE MEDICATION ADHERENCE

Stephanie O'Malley, Ph.D.
Yale University School of Medicine

Given the critical role of medication adherence to the success of a clinical trial, researchers have investigated means to enhance adherence, including educational, behavioral and technological strategies. The efficacy of these approaches will be presented and the potential value of personalizing adherence strategies based on the person's past history of medication adherence and on their adherence within the trial will be discussed. The use of new technologies, such as text messaging, to increase adherence and tailor interventions will also be illustrated.

GENERAL DISCUSSION
Thomas Laughren, M.D.

INDIVIDUAL RESEARCH REPORTS: BIPOLAR DISORDER AND CLINICAL ASSESSMENT
10:15AM – 11:15AM
INDIVIDUAL ABSTRACT:
VALACYCLOVIR IMPROVES COGNITION IN INDIVIDUALS WITH BIPOLAR DISORDER WHO ARE HSV-1 POSITIVE

Jennifer L. Payne, M.D.[1], Lea T. Drye, Ph.D.[2]
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Background: Recent studies have suggested that chronic, recurrent infections with herpes viruses may play a role in chronic mental illnesses such as schizophrenia and bipolar disorder. Further, previous studies have demonstrated that serological evidence of infection with HSV1 is predictive of cognitive impairment in bipolar disorder. Objective: We hypothesized that valacyclovir would reduce cognitive impairment in bipolar disorder by treating the herpes simplex infections that may be contributing to the cognitive impairment seen in some patients.
Methods: We randomized 60 outpatients meeting diagnostic criteria for DSM-IV Bipolar I or II disorder and testing positive for HSV-1 to either valacyclovir or matching placebo for sixteen weeks. Each subject demonstrated cognitive impairment at randomization by scoring less than 85 (one standard deviation from the normal range) on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). All subjects were maintained on a stable regimen of psychiatric drugs prescribed by their treating psychiatrist. The primary outcome was response defined as a 10 point or greater increase on the RBANS from randomization to study exit.
Results: 19 participants in the placebo arm finished 16 weeks of follow-up and three others had a second RBANS available at study exit. In the Valacyclovir arm, 16 finished 16 weeks of follow-up and 3 others had a second RBANS available at study exit. Using all available data, 3/22 (13.6%) responded in the Placebo arm and 10/19 (52.6%) responded in the valacyclovir arm. Comparing the proportion who responded using a two-tailed Fisher's exact test resulted in a p value of 0.017 thus demonstrating a statistically different response rate between the valacyclovir treated group compared to placebo.
Conclusions: We found that valacyclovir improved cognition compared to placebo in subjects with bipolar disorder, who were HSV-1 positive and who were cognitively impaired at baseline.

Learning Objectives:
- Participants will be able to identify the association between Herpes Simplex Virus 1 and cognitive symptoms in bipolar disorder.
- Participants will be able to describe the results of a double-blind, placebo controlled trial of valacyclovir on cognition in bipolar disorder.

Literature References:
- Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Ruslanova I, and Yolken RH: Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. Arch Gen Psychiatry 2003; 60:466-472
- Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Cole S, Krivogorsky B, and Yolken RH: Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder. Biol Psychiatry 2004; 55:588-593
- Dickerson FB, Boronow JJ, Stallings CR, Origoni AE, and Yolken RH: Reduction of symptoms by valacyclovir in cytomegalovirus-seropositive individuals with schizophrenia. Am J Psychiatry 2003; 160:2234-2236

INDIVIDUAL ABSTRACT:
AN INNOVATIVE METHOD FOR TRACKING CHANGES IN PRESCRIBED MEDICATION, CLINICAL DECISION MAKING, AND OUTCOME IN COMPARATIVE EFFECTIVENESS RESEARCH

Noreen A. Reilly-Harrington, Ph.D.[1], Louisa Sylvia, Ph.D.[2], Leah W. Shesler, B.A.[2], Terence A. Ketter, M.D.[3], Charles Bowden, M.D.[4], Joseph R. Calabrese, M.D.[5], Edward Friedman, M.D.[6], Michael Ostacher, M.D., M.P.H.[7], Dan V. Iosifescu, M.D., M.Sc.[8], Dustin Rabideau, B.A.[2], Michael E. Thase, M.D.[9], Andrew A. Nierenberg, M.D.[2]

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Background: Complex regimens of multiple medications are typically employed to manage bipolar disorder (BD)[1]. Clinicians "personalize" medication recommendations based on prior history, response and tolerability to current treatment, and consideration of adverse effects. This presentation describes the development and use of the Medication Recommendation Tracking Form (MRTF), a novel tool for capturing physician prescribing behavior and clinical decision making.

Method: The MRTF was developed by the Bipolar Trials Network and implemented in the Lithium Treatment Moderate Dose Use Study (LiTMUS), a comparative effectiveness study for BD, which randomized 283 patients to Lithium + optimized treatment (OPT) or to OPT alone [2]. The MRTF was used to assess frequency, types, and reasons for medication adjustments made by physicians. Changes in treatment were operationalized by the innovative metric Necessary Clinical Adjustments (NCA), defined as medication adjustments to reduce symptoms, optimize treatment response/ functioning, or to address intolerable side effects. NCAs served as a proxy for clinical effectiveness.

Results: While randomized treatment groups did not differ in rates of NCAs, remitters (defined as Clinical Global Impression - Bipolar Version Overall Severity (CGI-BP) ≤ 2) had significantly

fewer NCAs than non-remitters. Furthermore, there was evidence of a causal relationship between NCA count and remitter status, in that patients who had more NCAs during their previous visit had significantly lower odds of remitting at the current visit. There was also a relationship between symptom severity and NCAs at the subsequent visit. Specifically, for each one-unit increase in previous CGI-BP depression score and CGI-BP overall severity score, patients had an increased NCA rate of 13% and 15% respectively. Ten-unit increases in previous Montgomery Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) scores resulted in an 18% and 14% increase in rates of NCAs, respectively. With regard to psychosocial functioning, patients with fewer NCAs had increased quality of life and decreased functional impairment.

Conclusions: The MRTF is the first tool in psychiatry to track the types and reasons for medication changes and has important implications for training clinicians and examining clinical decision making. It has relevance for comparative effectiveness trials, which are designed to test real-world treatments, requiring the use of treatment arms that mimic care in community settings. The MRTF can advance current methodology by standardizing the reporting and rationale for medication adjustments and providing an innovative metric for clinical effectiveness.

Learning Objectives:
- Introduce a novel method for tracking prescriptive behavior and clinical decision making.
- Learn how the MRTF can serve as an innovative outcome for comparative effectiveness research

Literature References:
- Post RM, Denicoff KD, Leverich GS et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry. 2003 Jun;64(6):680-90; quiz 738-9.
- Nierenberg AA, Sylvia L, Leon AC, Reilly-Harrington N, Ketter TA, Calabrese JR, Thase ME, Bowden CL, Friedman ES, Ostacher MJ, Novak L, Iosifescu DV. Lithium treatment - moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. Clin Trials. 2009 Dec;6(6):637-48.

INDIVIDUAL ABSTRACT:
DIMENSIONAL ASSESSMENT OF MOOD-SPECTRUM PSYCHOPATHOLOGY IN INDIVIDUALS WITH BIPOLAR I, II AND UNIPOLAR DISORDER: CONTINUITIES AND DISTINCTIONS

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Objectives: Investigators argue about whether mood disorders are better understood as continuous spectra of psychopathology or discrete diagnostic entities ([1]). The MOODS-SR is a 161 item, lifetime, self-report, measure that evaluates manic and depressive symptoms, traits, and lifestyles in order to characterize affective psychopathology across continuous dimensions of depressive and manic-hypomanic dysregulation ([2]). The goal of the current study was to examine MOODS-SR scores in individuals meeting DSM IV criteria for bipolar (BP) I, II, and unipolar (UP) disorders to determine a) whether there were differences in MOODS-SR scores among the diagnostic groups and b) whether specific subscales of the MOODS-SR could be used to discriminate among these categorical diagnoses.

Methods: 634 participants (379 BP I, 130 BP II, 125 UP) enrolled in a clinical research program were included in the analyses. We compared previously established factors from the depressive component (depressive mood, psychomotor retardation, suicidality, drug/illness related depression, psychotic spectrum features, neurovegetative symptoms) and the manic-hypomanic component (psychomotor activation, creativity, mixed instability, sociability/extraversion, spirituality/mysticism/psychoticism, mixed irritability, inflated self-esteem, euphoria, wastefulness/recklessness) of the MOODS-SR across groups. We then applied classification tree analyses to a subset (females only because the UP sample were all female), n= 445, to identify subscales that could correctly categorize diagnostic groups.

Results: Pair-wise comparisons of mean MOODS-SR scores showed that all factors discriminated BP I and II from UP, but none except spirituality/mysticism/psychoticism discriminated BP I from BP II ($p < 0.05$). Classification tree analyses found that women with > 10 positive items on the psychomotor activation scale and >3 items on the spirituality scale had a 95% likelihood of having a diagnosis of BP I disorder. Excluding BP I's from the analyses, women endorsing >7 items on the psychomotor activation scale had a 83% likelihood of having BP II disorder.

Conclusions: Individuals with BP I and II disorders cannot be distinguished from one another using the MOODS-SR, suggesting continuity of these constructs across DSM IV diagnoses. On the other hand, MOODS-SR scores discriminate between BP and UP disorders. These findings suggest that both dimensional and categorical approaches may be important to understanding mood disorders, as the underlying constructs may have elements that are both continuous and discontinuous.

Learning Objectives:
- To examine dimensional measures of mood spectrum psychopathology in individuals meeting DSM-IV criteria for bipolar I, II and unipolar disorders
- To determine whether MOODS-SR factors can be used to discriminate among bipolar I, II, and unipolar disorders

Literature References:
- Cassano GB, Rucci P, Frank E, Fagiolini A, Dell'Osso L, Shear MK, et al. The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. American Journal of Psychiatry. 2004;161:1264-9.
- Dell'Osso L, Armani A, Rucci P, Frank E, Fagiolini A, Corretti G, et al. Measuring mood spectrum: comparison of interview (SCI-MOODS) and self-report (MOODS-SR) instruments. Comprehensive Psychiatry. 2002;43:69-73.

INDIVIDUAL ABSTRACT:
USE OF "DUAL" RATINGS CRITERIA TO IMPROVE SUBJECT SELECTION AND TRIAL OUTCOMES
Steven D. Targum, M.D.[1], Pamela C. Wedel, B.S.[2]
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We compared the "dual" scores from the Inventory of Depressive Symptoms (IDSc30) obtained by site-based clinician raters and centralized (site-independent) raters conducted during a double-blind, placebo-controlled study of patients with acute Major Depressive Disorder (trial CBM-IT-01; BCI NCT 007005003). At the baseline visit, centralized raters scored the total IDSc30 significantly lower than site-based raters (p= 0.027). In a post-hoc analysis, we examined whether a "dual" scoring concordance range applied as part of the randomization criteria could

affect the treatment outcome. Using a criterion of ≥ one standard deviation from the mean baseline IDSc30 as a cut-off, we selected a concordance range of ≤ 9 points scoring difference between site-based and centralized raters to exclude the most markedly discordant subjects from the analysis. This criterion identified 85 of the 114 subjects at week 6 (end of treatment) who had concordant "dual" baseline IDSc30 scores.

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

Learning Objectives:
- To explore the utility of external review to improve ratings precision
- To determine with "dual" concordance ranges can affect trial outcomes

Literature References:
- Fava M, Targum SD, Nierenberg AA, Bleicher LS, Carter TA, Wedel PC, Hen R, Gage FH, Barlow C. An Exploratory Study of Combination Buspirone and Melatonin SR in Major Depressive Disorder (MDD): A Possible Role for Neurogenesis in Drug Discovery, J Psychiat. Res. 46:1553-1563, 2012
- 2. Targum, SD, Little, JA, Lopez, E, DeMartinis, N, Rapaport, M, Ereshefsky, L. Application of external review for subject selection in a schizophrenia trial. J Clin Psychopharmacol., 32 (2): 825-826, 2012

INDIVIDUAL RESEARCH REPORTS: CHILDHOOD AND ADOLESCENT & SLEEP DISORDERS
10:15AM – 11:15AM
INDIVIDUAL ABSTRACT:
THE SLEEP EFFECTS OF LURASIDONE: A PLACEBO-CONTROLLED CROSS-OVER STUDY USING A 4-HOUR PHASE-ADVANCE MODEL OF TRANSIENT INSOMNIA

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Introduction: Lurasidone is an atypical antispychotic agent that is unique in being a potent 5HT-7 antagonist as well as D2 and 5HT-2A antagonist and 5HT-1A partial agonist and it is also without appreciable histaminergic or cholinergic receptor affinity. This is the first study of the sleep effects of this unique agent and it provides the first data on the sleep effects of antagonism of 5HT-7 receptors, the most potent pharmacologic effect of lurasidone. Blocking these recpetors, which are found in the hypothalamic suprachiasmatic nucleus, would be expected to modulate sleep and circadian function based on animal modesl but no studies of the sleep effects of a 5HT-7 antagonist have been carried out in humans.Methods: This was a two-site, 2-period, cross-over, polysomnograhic study involving 54 non-sleep-deprived, healthy volunteers without sleep complaints. Each subject underwent 2 treatment periods (order randomized) each consisting of two nights in the laboratory. On night one they went to bed at their usual bedtime. On night two they underwent a 4 hour advance of sleep phase and received either lurasidone 40 mg or placebo 30 minutes prior to lights out. The next morning, impariment

testing was carried out using the Visual Analogue Scale of Sleepiness, Digit Symbol Substitution Test, and Symbol Copying Test.Results: Lurasidone increased total sleep time, the primary outcome measure, by an average of 28.4 minutes vs. placebo (p<0.05). Lurasidone also significantly decreased wake time afdter sleep onset (WASO) and wake time after the final awakening (terminal WASO), and increased sleep efficiency, N2%, and N2 sleep time compared with placebo. No statistically significant effects were found with other sleep variables or any indices of next-morning impairment. Conclusion: Lurasidone's therapeutic effect in this transient insomnia paradigm on sleep maintenance, particularly at the end of the night without a sleep onset effect is unique and could reflect a sleep-phase delaying effect of 5HT-7 antagoism in humans. Lurasidone also has a uniquely therapeutic sleep/wake profile among antipsychotic agents. It is likely to be beneficial for the many patients with thought and mood disorders with disturbed sleep, particularly those with problems with sleep maintenance and early morning awakening.

Learning Objectives:
- Understand the effects of lurasidone on sleep/wake function
- Appreciate the potential role of 5HT7 antagonism in mediating the effects of lurasidone on sleep

Literature References:
- Ishibashi, T., et al., Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther, 2010. 334(1): p. 171-81.
- Lovenberg, T.W., et al., A novel adenylyl cyclase-activating serotonin receptor (5-HT7) implicated in the regulation of mammalian circadian rhythms. Neuron, 1993. 11(3): p. 449-58

INDIVIDUAL ABSTRACT:
EXTENDED OXYTOCIN TREATMENT OF CHILDREN WITH AUTISTIC DISORDER

Terrence C. Bethea, M.D.[1], Linmarie Sikich, M.D.[2], Cheryl Alderman, B.S., CCRP[3], Jacqueline L. Johnson, Dr.PH[4], Lindsey M. Hazzard, MSW[2], Simon G. Gregory, Ph.D.[5]
[1]University of North Carolina at Chapel Hill, [2]UNC-Chapel Hill, [3]ASPIRE Program, University of North Carolina at Chapel Hill, [4]UNC Chapel Hill, [5]Duke University

Background: Animal studies have demonstrated that oxytocin is important in regulating affilliative and nurturing behaviors in some species and that administration of a single dose of oxytocin to nonhuman primates enhances generosity and awareness of social hierarchies. Single doses of oxytocin in adults and adolescents with autism have been demonstrated to improve awareness of social behaviors and recognition of emotion. In adults with Fragile X, a single 24 IU dose of oxytocin improved eye contact. This clinical trial examines the effects of repeated doses of oxytocin given for a sustained period of time in children with autism.

Objectives: Our aim was to determine if extended treatment with intranasal oxytocin would be tolerated by children with autism across the pediatric age range and to characterize any changes in social functioning associated with treatment.

Methods: We randomly assigned children ages 3 to 17 years with autistic disorder (DSM IV 299.0) confirmed by ADOS to 8 weeks of twice daily (AM and afternoon) treatment with flexibly dosed intranasal oxytocin or matched placebo. Subsequently, all participants received twice daily oxytocin for 8 weeks. Participants were assessed with the Aberrant Behavior Checklist (ABC), the Social Reciprocity Scale(SRS), the Pervasive Developmental Behavior

Inventory (PDD BI), the Vineland Adaptive Behavior Scales – 2 and Stanford-Binet. Adverse events were systematically elicited.

Results: 25 children, mean age 10.3 ± 4.4 (SD) years, were randomized: 12 to oxytocin and 13 to placebo. Eleven children were nonverbal and fourteen had fluent speech. Oxytocin was well tolerated with the exception of one participant withdrew within 2 weeks of treatment with oxytocin due to worsening insomnia and agitation. Worsening oppositionality, aggression, irritability, poor concentration and gastrointestinal disorders were all more common during the course of placebo treatment than oxytocin treatment. Those treated with oxytocin showed reductions in many, but not all, measures of social functioning: ABC-Social Withdrawal -2.0(1.0 SE) with oxytocin versus -1.3(1.8) with placebo; PDD-BI Social Deficit Score -2.8(1.6) with oxytocin versus -1.5(2.0)with placebo; SRS Awareness -4.4(2.9) with oxytocin versus -2.1(3.9) with placebo, SRS Motivation -5.8(3.9) with oxytocin versus -2.1(3.5) with placebo, SRS total -5.1(2.3) with oxytocin versus -3.9(3.3) with placebo. They also had a significant reduction in ABC-Irritability -3.4(0.9) with oxytocin versus -1.7(1.7) with placebo. Benefits continued to acrue during the 8 weeks of open oxytocin treatment.

Conclusions: Oxytocin was well tolerated by most children in the trial over 8 weeks of sustained treatment. It appeared to have benefit for reducing irritability and improving some aspects of social functioning. Larger scale trials of sustained intranasal oxytocin treatment in children with autism are needed to fully evaluate its safety and establish its efficacy for improving social functioning.

Learning Objectives:
- Long term effects of intranasal oxytocin administration in children and adolescents with autism
- Characterize any change in specifically in social functioning after intranasal oxytocin treatment in children and adolescents with ASD

Literature References:
- Veening, JG et al. Oxytocin-messages via the cerebrospinal fluid: Behavior effects: a review. Physiology and Behav. 2010. 101:193-210
- Gregory, S.G., et al., Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. BMC Med 2009. 7:62-75

INDIVIDUAL ABSTRACT:
RANDOMIZED, CONTROLLED, PHASE 2 TRIAL OF STX209 FOR SOCIAL FUNCTION IN AUTISM SPECTRUM DISORDER (ASD)

Paul Wang, M.D.[1], Linmarie Sikich, M.D.[2], Raun D. Melmed, M.D.[3], Jana von Hehn, Ph.D.[4], Karen Walton-Bowen, MSc, C.Stat, C.Sci[4], Maryann Cherubini, B.S., MFT[4], Peter Zarevics[4], Randall L. Carpenter, M.D.[4], Mark Bear, Ph.D.[5], Noriko Kuriyama, MA[1], Edwin Cook, M.D.[6], Jeremy Veenstra-VanderWeele, M.D.[7]

[1]Seaside Therapeutics, Inc., [2]UNC-Chapel Hill, [3]Southwest Autism Research and Resource Center, [4]Seaside Therapeutics, [5]MIT/HHMI, [6]University of Illinois at Chicago, [7]Vanderbilt University

Background: STX209 (arbaclofen) is a selective GABA-B agonist associated with behavioral and disease-modifying effects in animal models of fragile X syndrome (FXS). It is hypothesized to modulate mGluR5 signaling and to augment inhibitory neurotransmission.

In an open-label study of ASD, STX209 was associated with significant improvement on the ABC-Lethargy/Social Withdrawal (ABC-LSW) subscale, the Social Responsiveness Scale, and

the Vineland Adaptive Behavior Scales (VABS) Communication score. In a placebo-controlled trial in 63 subjects with fragile X syndrome (FXS), STX209 was associated with significant improvement on the ABC-Social Avoidance subscale, which is specifically validated in FXS. VABS Socialization scores also improved in the subgroup of 27 subjects with more severe social impairments.

Purpose: To examine the efficacy, safety, and tolerability of STX209 in patients with ASD, age 5-21 years.

Methods: A 12 week RCT was conducted in subjects with Autistic Disorder, Asperger's Disorder, or PDD-NOS and with a score ≥8 on the ABC-LSW. Up to 2 concomitant psychoactive medications were allowed, excluding those with anxiolytic or antipsychotic effects. Study drug was titrated over 4 weeks, followed by fixed dosing for 8 weeks. Efficacy assessments included the ABC subscales, CGI-I, CGI-S, and VABS Social and Communication scales.

Results: 150 subjects were randomized, and 130 completed the study, with 10 (8 STX209, 2 placebo) discontinuing due to adverse events, which were generally behavioral. There were 2 serious adverse events (suicidal ideation on STX209; anaphylaxis on placebo) and 1 non-serious event of suicidal ideation on placebo. STX209 was well-tolerated overall, with a 9% incidence of somnolence.

On the primary endpoint, the ABC-LSW subscale, subjects on STX209 and placebo showed similar improvement (change from baseline -5.4±0.78 vs. -6.0±0.75, LS mean±SEM, p=0.518). On the CGI-S, subjects improved significantly more on STX209 (-0.6±0.10 vs. -0.2±0.10, p=0.006). On the other secondary endpoints, results favored STX209 numerically, but did not reach statistical significance. In a post-hoc analysis among subjects whose VABS assessments were conducted by the same clinican and caregiver (n=96) as specified in the protocol, there was greater improvement on VABS-Socialization on STX209 (7.2±1.40 vs. 1.8±1.27, p=0.006). This effect was notably larger in subjects with IQ≥70.

Conclusions: STX209 was well-tolerated and shows potential for clinically-meaningful improvements in social function. New, prospective studies are required to confirmation these findings.

Learning Objectives:
- Explain the rationale for STX209 in autism
- Describe the potential effect of STX209 in autism

Literature References:
- Berry-Kravis E, eat al: Effects of STX209 (Arbaclofen) on Neurohehavioarl Function in Children and Aduls with Fragile X Syndrome: A Randomized, Controlled, Phase 2 Trial. Sci Trans Med 2012; 4: 152ra127.
- Dolen G, Bear MF; Fragile X syndrome and autism: from disease model to therapeutic targets. J Neurodev Disord: 1:133-40.

INDIVIDUAL ABSTRACT:
EFFECT OF D-CYCLOSERINE (DCS) ON THE CORE SOCIAL DEFICIT IN HIGH-FUNCTIONING ADOLESCENTS AND YOUNG ADULTS WITH ASD
Maria Urbano, M.D. , Stephen Deutsch, M.D., Ph.D., Leonore Okwara, MPH, Kathrin Hartmann, Ph.D.
Eastern Virginia Medical School

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders with core impairments in social communication and repetitive, stereotypic behaviors. Impaired sociability is especially difficult for adolescents and adults with ASDs, whose focus is on independent living. No medications for this core symptom domain have been approved.

Mice with diminished expression and affinity of the NR1 subunit of the NMDA receptor for glycine, the obligatory co-agonist with glutamate, show impaired sociability. The impaired sociability of the Balb/c mouse, a model of ASDs with altered endogenous tone of NMDA-mediated neurotransmission, improved after treatment with DCS, a partial glycine$_B$ agonist[1]. DCS works cooperatively with L-glutamate to promote NMDA receptor-gated Ca^{2+} conductance. Additionally, NMDA receptor activation is a regulator of mTOR activity, an important serine/threonine kinase that serves as a point of convergence in *Ras* and *PI3K* signaling pathways.

DCS has been reported to diminish social withdrawal in some children with ASDs[2]. We conducted a 10-week randomized trial comparing the prosocial effects of single daily (50 mg/day) and interval (50 mg/week) doses of DCS in 20 male and female subjects (ages 14-25) with ASD and an IQ >70. Subjects participated in four visits, with the final visit being a two week follow-up off drug. DCS was well tolerated.

Subject outcomes were measured using the Social Responsiveness Scale (SRS) and the Aberrant Behavior Checklist (ABC). Linear mixed effects models were fit to the SRS and each of the five ABC subscales to test for linear time trends as well as differences in response curves between the two dosing strategy groups (DSGs). A common time trend for both DSGs was found to be significant for the SRS ($p = 0.003$), indicating an overall increase in social responsiveness for both groups over time. Similarly, ABC subscale II for lethargy/social withdrawal showed a trend towards improvement ($p = .024$), but did not meet a significance threshold of $\alpha = 0.05$ after adjusting for multiple comparisons across all ABC subscales. A computed Spearman correlation between ABCII and SRS was $r=.64$ indicating moderate agreement between them. When collapsing results from both DSGs, there was a clear improvement from baseline in SRS with a mean decrease of 17.9 points across time on drug (95% CI: 15.3, 20.6).No differences in response curves between dosing strategies were observed for either the SRS or ABC subscales.

DCS holds promise as a component of a multimodal, interdisciplinary treatment plan for the core social deficit in ASDs, which may enhance the effectiveness of other psychotherapeutic interventions. Understanding the neuropsychopharmacology of the mechanism of action of DCS may further elucidate the pathways involving L-glutamate and NMDA receptor activity. Conceivably, at least some of the therapeutic effect of DCS in ASD may relate to its influence on the activity of mTOR.

Our findings support the efficacy of both DCS DSGs to improve social communication in ASDs. This study supports the use of the SRS and the ABC as primary outcomes measures. Given the above findings, additional medication trials are warranted.

Learning Objectives:
- Familiarize the audience with the role of NMDA receptor activation in regulation of sociability
- Familiarize the audience with D-cycloserine's potential therapeutic mechanism of action in ASDs

Literature References:
- Deutsch SI, Burket JA, Jacome LF, Cannon WR, Herndon AL: D-Cycloserine improves the impaired sociability of the Balb/c mouse. Brain Res Bull 2011; 84: 8-11

- Posey DJ; Kem Dl; Swiey NB; Sweeten TL; Wiegand RE; McDougle CJ: A Pilot Study of D-Cycloserine in subjects with autistic disorder. Am J Psychiatry 2004; 161: 2115-2117

INDIVIDUAL RESEARCH REPORTS: DEPRESSION
10:15AM – 11:15AM
INDIVIDUAL ABSTRACT:
THE FUTURE OF PSYCHIATRIC MEASUREMENT

Robert D. Gibbons, Ph.D.[1], David J. Kupfer, M.D.[2], Ellen Frank, Ph.D.[3], Paul A. Pilkonis, Ph.D.[4], David J. Weiss, Ph.D.[5], Tara Moore, M.A., M.P.H.[6]
[1]University of Chicago, [2]University of Pittsburgh School of Medicine, [3]Western Psychiatric Institute and Clinic; University of Pittsburgh School of Medicine, [4]University of Pittsburgh, [5]University of Minnesota, [6]Western Psychiatric Institute and Clinica/UPMC

Mental health measurement has been based primarily on subjective judgment and classical test theory. Typically, impairment level is determined by a total score, requiring that all respondents be administered the same items. An alternative to full scale administration is adaptive testing in which different individuals may receive different scale items that are targeted to their specific impairment level. Within adaptive testing, individuals' initial item responses are used to determine a provisional estimate of their standing on the measured trait (e.g., depression, anxiety) to be used for subsequent item selection. This form of testing has recently emerged in mental health research. Based on item response theory (IRT) procedures, estimates of items (e.g., difficulty, discrimination) and individuals (e.g., severity of depression) can be obtained to more efficiently identify suitable item subsets for each individual. This approach to testing is referred to as computerized adaptive testing (CAT) and is immediately applicable to mental health measurement problems. We have developed a CAT depression inventory (CAT-DI), based on multidimensional IRT, well suited to mental health constructs, that can be administered adaptively such that each individual responds only to those items that are most informative for assessing his/her level of depression. The net result is that an individual is administered a small, optimal number of items from a much larger "bank" of items, without loss of measurement precision. The shift in paradigm is from small fixed length tests with questionable psychometric properties to large item banks from which an optimal small subset of items is adaptively drawn for each individual, targeted to their level of impairment. Rather than fixing the number of items and allowing measurement precision to vary, we fix measurement precision and allow the items to vary. For longitudinal studies, the previous impairment estimate is then used as a starting point for the next adaptive test administration, further decreasing the number of items needed to be administered. Applications in the areas of screening depression in primary care, child psychiatry, global health, randomized controlled trials, molecular genetics, computerized adaptive diagnosis, and psychiatric epidemiology are described.
Results to date reveal that depressive severity can be measured using an average of only 12 items (2 minutes) from a bank of 400 items, yet maintains a correlation of r=0.95 with the 400 item scores. Using an average of only 4 items (1 minute) we have derived a diagnostic screening test for major depressive disorder which has sensitivity of 0.95 and specificity of 0.87, where for the same subjects, sensitivity for the PHQ-9 is only 0.70 with similar specificity and requires more than twice the number of items.

Learning Objectives:
- Learn about item response theory and the bi-factor model

- Learn about computerized adaptive testing
- Discuss improved mental health measurement

Literature References:

- Gibbons RD, et al. The CAT-DI: A computerized adaptive test for depression. Archives of General Psychiatry, 2012;69:1104-1112 .
- Gibbons RD and Hedeker D, Full information item bifactor analysis. Psychometrika,
- Gibbons RD, et al. Using computerized adaptive testing to reduce the burden of mental health assessment. *Psychiatric Services* 2008;59:361–68. Gibbons RD, et al. Full-information item bi-factor analysis of graded response data. *Applied Psychological Measurement,* 2007;31:4–19.

INDIVIDUAL ABSTRACT:
DIFFERENCES IN COGNITIVE FUNCTION BETWEEN 5HT1A GENOTYPES IN A LARGE SAMPLE OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Keith Wesnes, Ph.D.[1], Seth Hopkins, Ph.D.[2], Kenneth s. Koblan, Ph.D.[3]
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Background: Bosia et al (2011) studied the effects of the 5-HT1A-R genotype on cognition in schizophrenic patients , and identified that the 5-HT1A-R C/C genotype was associated with significantly higher scores on a Picture Sequencing Task than the C/G and G/G genotypes. The purpose of this study was to determine whether 5-HT1A-R genotype had an influence on the profile of cognitive function in patients with major depressive disorder (MDD).

Methods: The study sample was 455 MDD patients between the ages of 18 and 55 years who met DSM-IV criteria for MDD, with current-episode duration of at least 1 month but not longer than 12 months. The patients underwent 5-HT1A-R genotyping and performed a selection of automated tests of attention, information processing, executive control, working and episodic memory from the CDR System. The volunteers had on previously performed the entire 20 minute sequence of tests twice in order to overcome practice and familiarity effects. Performance in various domains was contrasted between the three 5-HT1A-R genotypes using ANOVA.

Results: There were no differences between the three genotypes on HAM-D-17 ($p=0.92$), Sheehan Disability Scale total score ($p=0.52$) or age ($p=0.96$). Significant differences were seen on accuracy measures from 2 working memory (articulatory and spatial) and 4 episodic memory tasks (verbal: immediate recall, delayed recall and recognition; picture recognition). These were seen on validated factor scores for working memory ($p=0.047$), episodic memory ($p=0.014$) and a combined score ($p=0.006$). No effects were seen for measures of sustained or focussed attention, information processing speed or attentional fluctuations ($p=0.34$ to 0.98). Neither was an effect seen for the speed of retrieval of information in the working memory and episodic recognition tasks ($p=0.55$). For the combined working end episodic memory accuracy score, the C/C homozygotes scored significantly higher (66.8%; 95% CI 64.5,69.1) than both the C/G heterozygotes (62.4%; 95% CI 60.8,63.9) and the G/G homozygotes (63.3%; 95% CI 61.2, 65.4), the p values being 0.0016 and 0.0246 respectively.

Discussion & Conclusions: These are to our knowledge the first data in MDD which show a difference in cognitive function between the three 5HT1A-R genotypes. The finding that the C/C genotype was selectively superior to the other genotypes on the ability to the hold and retrieve information in working and episodic memory, while not showing differences in retrieval speed or on various measures of attention and information processing is clearly worthy of future attention; particularly as there were no differences between the genotypes in either depression or disability

scores. Further work will be conducted to investigate the pattern of changes to cognitive function in the three genotypes following antidepressant therapy.

Learning Objectives:
- Learn about 5HT1A polymorphisms in MDD and their relationship to disability and disease severity
- Appreciate the differences in domains of cognitive function associated with 5HT1A polymorphisms in MDD

Literature References:
- Bosia M et al (2011). Effect of 5-HT1A-receptor functional polymorphism on Theory of Mind performances in schizophrenia. Psychiatry Research 188: 187–190.
- Beste C et al (2010). Functional 5-HT1a Receptor Polymorphism Selectively Modulates Error-Specific Subprocesses of Performance Monitoring. Human Brain Mapping 31:621–630

INDIVIDUAL ABSTRACT:
THE REMISSION FROM DEPRESSION QUESTIONNAIRE AS AN OUTCOME MEASURE IN THE TREATMENT OF DEPRESSION
Mark Zimmerman, M.D.
Brown University

Background: The Remission from Depression Questionnaire (RDQ) was designed to capture multiple domains considered by patients to be relevant to the construct of remission. The present study is the first to examine the validity of the RDQ as an outcome measure. We examined whether each of the subscales of the RDQ was sensitive to change, and compared the scale as a measure of outcome to the Hamilton Depression Rating Scale (HAMD) and Quick Inventory of Depressive Symptomatology (QIDS).

Methods: One hundred fifty three depressed patients who presented for treatment, or who were in ongoing treatment and had their medication changed due to lack of efficacy, were evaluated at baseline and at 3 month follow-up. In addition to the RDQ, the patients completed the QIDS, and they were rated on 17-item HAM-D.

Results: On each scale the patients showed significant levels of improvement from baseline to 3 months. The effect size of the RDQ total score was similar to the effect sizes of the HAMD and QIDS. The coping and psychosocial functioning subscales of the RDQ had lower effect sizes than the other subscales. Both the RDQ and QIDS were significantly associated with patients self-reported remission status. However, the RDQ remained significantly associated with remission status after controlling for QIDS scores, whereas the QIDS was not associated with remission status after controlling for RDQ scores.

Discussion: The RDQ is as sensitive to change as are purely symptom-based scales such as the QIDS and HAMD. Moreover, compared to the QIDS, the multidimensional RDQ is more closely aligned with patients' self-perception of their remission status. The RDQ allows clinicians and researchers to gain a broader perspective of depressed patients' status than purely symptom measures, and is more consistent with a biopsychosocial approach towards the treatment of depression.

Learning Objectives:
- To become more familiar with a new type of measure of outcome in treating depression that measures constructs patients consider important in treating depression.

- To become aware that different outcome variables have different effect sizes when evaluating treatment for depression.

Literature References:
- Zimmerman M, McGlinchey J, Posternak M, Friedman M, Attiullah N, Boerescu D. How should remission from depression be defined? The depressed patient's perspective. Am J Psychiatry 2006;163:148-150.
- Zimmerman M, Martinez J, Attiullah N, Friedman M, Toba C, Boerescu D, Ragheb M. A new type of scale for determining remission from depression: The Remission from Depression Questionnaire. J Psychiatr Res 2013;47:78-82.

INDIVIDUAL ABSTRACT:
METHYLPHENIDATE AUGMENTATION OF CITALOPRAM IS EFFECTIVE IN REDUCING DEPRESSION SEVERITY AND IMPROVING COGNITION IN GERIATRIC DEPRESSION: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL
Helen Lavretsky, M.D.
UCLA Semel Institute for Neuroscience and Human Behavior

Objective: Enhanced and accelerated antidepressant treatment response may be particularly beneficial for older patients given low remission rates and high rates of suicidal ideations and cognitive impairment, yet there are few data to inform clinical practice. We evaluated the potential of methylphenidate to accelerate and enhance antidepressant response to citalopram in elderly depressed patients with respect to clinical and cognitive outcomes.
Methods: 133 elderly participants with major depression were treated in a 16-week double-blind placebo controlled trial of methylphenidate (MPH) augmentation of citalopram (CIT) (N=43) compared to CIT and placebo (PBO) (N=45) and MPH and PBO (N=45). We compared differences on remission rates, change scores in depression and measures of apathy, anxiety, health related quality of life, and cognitive measures using multivariate analyses and mixed regression models.
Results: Three groups do not differ significantly in any of the demographic measures. All 3 groups show significant changes in the severity of depression as measured by the Hamilton Depression Rating scale (HAM-D) and Montgomery- Asberg Depression rating scale (MADRS)(P<0.0001). However, the improvement in depression severity as measured by HAMD and MADRS was more prominent in the MPH+CIT group compared to MPH+PBO and CIT+PBO (P<0.001). The improvement in the SF-36 wellbeing scale score was greater in the MPH+CIT and CIT+PBO groups compared to MPH+PBO (P<0.01). However, CIT+ PBO group demonstrated worsening on the cognitive measures of executive function compared to both MPH groups (P<0.001), and CIT+MPH group showed greater improvement in measures of verbal memory (CVLT) compared to the MPH+PBO group (P<0.01).The three groups did not show differences on the change scores in measures of apathy, SF-36 energy scale score, and mini-mental scale Examination score (MMSE). Only 16 subjects dropped out due to side-effects with only 2 dropping out in the MPH+CIT group. The combination MPH+CIT was overall better tolerated compared to two comparison groups.
Conclusions: Combined treatment with citalopram and methylphenidate demonstrated an improved response profile in the mood and cognitive measures compared to either drug alone, and appears to be a viable option for accelerating and enhancing antidepressant response in elderly depressed patients that may be limited by individual tolerability of the side-effects.
Learning Objectives:

- To discuss the clinical and cognitive outcomes of the double- blind placebo-controlled trial of methylphenidate augmentation of citalopram in geriatric depression.
- To discuss safety profile of the combined use of methylpehnidate and citalopram compared to either drug used alone.

Literature References:
- Lavretsky H et al.. The effects of the dopamine and serotonin transporter polymorphisms on clinical features and treatment and treatment response in geriatric depression: a pilot study. Int J Geriatr Psychiatry. 2008 Jan;23(1):55-9.
- Lavretsky H et al. Methylphenidate-enhanced antidepressant response to citalopram in the elderly: a double-blind, placebo-controlled pilot trial. Am J Geriatr Psychiatry. 2006 Feb;14(2):181-5.

INDIVIDUAL RESEARCH REPORTS: SCHIZPPHRENIA AND CLINICAL TRIAL METHODOLOGY
10:15AM – 11:15AM
INDIVIDUAL ABSTRACT:
CIRCADIAN RHYTHMS IN COGNITIVE FUNCTIONING AMONG PATIENTS WITH SCHIZOPHRENIA: IMPACT ON SIGNAL DETECTION IN CLINICAL TRIALS OF PRO-COGNITIVE THERAPIES

Michael R. Hufford, Ph.D.[1], Vicki G. Davis, DrPH, Biostatistics[2], Richard Keefe, M.D.[3]
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Background: Circadian rhythms exert changes in cognitive functioning over the course of the day. Patients with schizophrenia are known to have profoundly disturbed circadian rhythms that can affect their cognitive functioning. Diurnal variations in cognitive functioning were analyzed by examining the impact of time of day on baseline composite MATRICS Consensus Cognitive Battery (MCCB) scores. Next, post hoc exploratory analyses were conducted in two Phase 2 clinical trials to examine whether taking into account consistency in the timing of neurocognitive administrations between the baseline and endpoint visits could affect signal detection.

Methods: For the diurnal variation analyses, 1,971 baseline MCCB assessments were aggregated across 8 separate schizophrenia clinical trials. The assessments were divided into 2-hour time intervals based on the start-time of the assessments (varying from 8am and 5pm) and then analyzed for differences by time interval. Next, two Phase 2 schizophrenia clinical trials were used to explore the impact of diurnal variation on pro-cognitive signal detection. We separated subjects into those with consistent ($\pm$1hr) versus inconsistent (>1hr) timing of neurocognitive battery administrations between their baseline and endpoint visits, and then compared the subgroups.

Results: Time of day exerted a significant effect on baseline composite MCCB scores ($p=.0009$), with composite scores varying more than 7 points over the course of the day. Follow-up contrasts with Bonferroni correction for multiple comparisons revealed significant differences among multiple temporal epochs. Next, analyses examined whether taking into account consistency in the time of day of neurocognitive administrations between the baseline and endpoint visit could affect signal detection. The first clinical trial was a 12-week placebo-controlled trial of an add-on therapy for cognition using the MCCB among subjects with schizophrenia stabilized on antipsychotic therapy recruited from the US (n=170). These analyses revealed that the treatment effect continued to favor drug over placebo for subjects with consistent assessment timing, whereas no trend was evident among subjects with inconsistent

timing. The second clinical trial was of a broad-spectrum antipsychotic used to treat acutely ill subjects for 6-weeks among patients with schizophrenia recruited from the US, India, and Romania (n=363). Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS). These analyses revealed that the consistent timing group showed a more robust treatment response as compared to the inconsistent timing group.

Conclusions: Cognitive functioning ebbs and flows over the course of the day. Maintaining consistency in the time of day of neurocognitive administrations between visits can help to enhance signal detection in clinical trials of pro-cognitive therapies.

Learning Objectives:
- Understand how circadian rhythms produce diurnal variations in neurocognitive performance over the course of the day
- Understand how taking into account diurnal variation can increase effect sizes and placebo separation for pro-cognitive agents in clinical trials

Literature References:
- Schmidt C., et al. (2007). A time to think: Circadian rhythms in human cognition. Cognitive Neuropsychology, 24, 755-789.
- Blatter, K. & Cajochen, C. (2007). Circadian rhythms in cognitive performance: methodological constraints, protocols, theoretical underpinnings. Physiology & Behavior, 90, 196-208.
- Bromundt, V. et al. (2011). Sleep-wake cycles and cognitive functioning in schizophrenia, The British Journal of Psychiatry, 198, 269-276.

INDIVIDUAL ABSTRACT:
PERSPECTIVES ON LONG-ACTING INJECTABLE ANTIPSYCHOTICS FOR SCHIZOPHRENIA: CONSIDERATION OF ETHNIC AND CULTURAL/RACIAL DIFFERENCES IN PLANNING INDIVIDUAL TREATMENT

Rimal B. Bera, M.D.[1], Steven G. Potkin, M.D.[2], Donna Zubek, BSN, MBA[3], Gina Lau, PharmD[3]
[1]University of California, [2]Department of Psychiatry and Human Behavior School of Medicine University of California, Irvine, [3]Otsuka America Pharmaceutical, Inc.

Purpose: Long-acting injectable (LAI) antipsychotics in naturalistic settings improve treatment outcomes in patients with schizophrenia versus oral agents. However, LAIs are underutilized and are often reserved for only those patients who are late in the course of illness and/or nonadherent to pharmacotherapy. Multiple studies have found cultural/racial differences in LAI prescription patterns. This study examined prescriber-patient interactions to investigate the impact of cultural/racial differences among patients with schizophrenia on perceptions towards LAIs and their use.

Methods: Linguists analyzed 120 prescriber-patient conversations about patient attitudes toward LAIs in selected cultural/racial subgroups (Caucasian [CA], Hispanic [HS], African-American [AA]; n=40 per group). Patient responses within and between cultural/racial subgroups were evaluated to identify similarities and differences in LAI conceptualization and attitudes.

Results: Most patients were male and had ≥10-year history of schizophrenia and the mean age across groups was similar (early 40s). Overall, approximately one-third of patients were either LAI naïve (35/120 [29%]), on LAIs at the time of the study (38/120 [32%]), or on oral agents at the time of the study (47/120 [39%]). Of the 35 LAI-naïve patients who were offered LAIs, 9% (3/35) responded favorably to the idea of LAI treatment, 46% (16/35) were neutral/passive with regard to treatment, and 46% (16/35) viewed this treatment as unfavorable/concerned (includes

those that declined treatment). Although the sample size in this analysis is limited, ≥50% of CA (7/14 [50%]) and AA (10/16 [63%]) patients were favorable or neutral to the prospect of treatment, compared with a minority of HS patients (2/5 [40%]). Among patients expressing their treatment goals (68/120 [57%]), 2 types of responses were recorded: control of positive/negative symptoms and discomfort control (insomnia, anxiety). Patients who focused on positive/negative symptom control generally expressed positive attitudes towards LAIs, whereas discomfort control was associated more with refusal to start or restart an LAI. HS patients seemed more focused on discomfort control (12/18 [67%]) versus symptom control, whereas the CA and AA patients were more equally distributed with respect to treatment orientations. Patients presenting with strongly disordered thinking were also more likely to focus on treating discomfort concerns (insomnia/anxiety). Dislike of needles was more pervasive in AA patients than HS or CA patients.

Conclusions: Among LAI-naïve patients, equal numbers were unfavorable/concerned (includes those that declined treatment) or were neutral/passive with regard to treatment, while a minority of patients responded favorably to the idea of LAI treatment. Subgroup analyses suggested that CA and AA patients may be more open to the prospect of LAI treatment compared with HS patients. However, it is important to note the limited sample size of this analysis, which precludes the ability to draw any cultural/racial-specific conclusions.

Learning Objectives:
- Compare the perspectives of Caucasian, Hispanic, and African-American patients regarding long-acting injectable antipsychotics for schizophrenia.
- Improve sensitivity toward the specific goals and concerns expressed by patients within each ethnic group and across groups.

Literature References:
- Horvitz-Lennon et al. The effect of race-ethnicity and geography on adoption of innovations in the treatment of schizophrenia. Psychiatr Serv 2012;63:1171-1177
- Aggarwal et al. Race and long-acting antipsychotic prescription at a community mental health center: a retrospective chart review. J Clin Psychiatry 2012;73:513-5173

INDIVIDUAL ABSTRACT:
USING PHARMACOKINETIC SAMPLING TO IDENTIFY PATIENT CHARACTERISTICS THAT PREDICT MEDICATION COMPLIANCE IN SCHIZOPHRENIA CLINICAL TRIALS
George M. Haig, PharmD, MBA, Earle E. Bain, M.D., Deli Wang, M.D., Ph.D., Ahmed Othman, Ph.D.
AbbVie

Medication compliance in schizophrenia clinical trials is traditionally documented by pill counts or patient interviews. Discordance with these methods and actual compliance has been well documented. Noncompliance in clinical trials limits the ability to answer scientific questions. The objective of this report is to characterize the pattern of noncompliance using pharmacokinetic sampling as a measure of compliance and to identify baseline characteristics that predict poor compliance in schizophrenia clinical trials.

Two multicenter trials in stable subjects with schizophrenia were conducted at approximately 45 sites in the United States. Both investigated the procognitive effects of novel investigational compounds as add-on therapy to antipsychotics. The same design was used in both trials, with 1 placebo and 2 active dose groups (planned N=70/group; total N=420 for both trials). Both study

drugs had long plasma elimination half-lives. Study medication was administered once daily. Trial duration was 12 weeks, with clinic visits scheduled every 2 weeks. Blood samples for plasma drug concentration determinations were collected at 6 post baseline visits. Only samples from subjects in active treatment groups were analyzed for compliance. A subject was defined as either compliant or noncompliant at a given visit, depending on the magnitude of departure of the plasma concentration observed at that visit from the trough concentration predicted for that dose group.

Study sites attested that at least 96% subjects for each visit administered >70% of study medication based on the pill counts method. Examination of the individual plasma concentrations at the different visits indicated that approximately 40% of the subjects were noncompliant (at 1 or more visits) and approximately 20% of all subjects were consistently noncompliant (at 3 visits or more). Compliance results were consistent across the two trials. Step-wise logistic regression analysis was used to evaluate a number of baseline and demographic variables, including sex, race, age, baseline PANSS score, baseline MCCB score, duration of illness, and living situation, to predict subjects who were most likely to be noncompliant.

These data indicate the magnitude of noncompliance in the schizophrenia population using quantitative methods and provide a basis for which to measure improvement in future clinical trials.

Learning Objectives:
- To describe the magnitude and pattern of noncompliance in two large schizophrenia clinical trials
- To understand the baseline patient characteristics that predict noncompliance

Literature References:
- Fialkoa L, Garetya P, Kuipersa E, et. al. A large-scale validation study of the Medication Adherence Rating Scale (MARS). Schizophrenia Res 2008;100(1–3):53–59
- Lindenmayer JP, Liu-Seifert H, Kulkarni P, et. al. Medication non-adherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. J Clin Psych 2009;70(7):990-996
- Dunbar-Jacob J, Sereika S, Houze M, et.al. Accuracy of measures of medication adherence in a cholesterol-lowering regimen. West J Nurs Res. 2012 August; 34(5): 578–597

INDIVIDUAL ABSTRACT:
CAN AN ELECTRONIC PATIENT-REPORTED OUTCOME DEVICE BE SUCCESSFULLY USED IN A MULTICENTER TRIAL IN PATIENTS DIAGNOSED WITH SCHIZOPHRENIA?
Virginia L. Stauffer, PharmD, Bruce Kinon, M.D., Simin Baygani, M.S., Judith Krikke-workel, Ph.D.
Eli Lilly and Company
Background: A patient-reported outcome (PRO) is any health condition status report directly from the patient, without interpretation and may potentially be used in product labeling. The use of PROs has been employed in a variety of disease states; however use in schizophrenia has generally been limited because of perception of poor patient adherence and compliance. This presentation will describe patient compliance of an electronic PRO (ePRO) device in the assessment of the primary outcome in a schizophrenia trial.

Methods: This was a 6-week, multicenter, randomized withdrawal, placebo-controlled trial to determine if pomaglumetad methionil, a metabotropic glutamate 2/3 receptor agonist, was likely to produce signs and symptoms suggestive of physical dependence when discontinued abruptly following an acute treatment trial in patients with schizophrenia. Outpatients 18 to 65 years of age requiring a modification or initiation of antipsychotic medication and willing to use the ePRO device were eligible. Patients received 4 weeks of open-label study drug then completers were randomized to stay on study drug or switch to placebo for 2 weeks. The primary outcome measure was the Discontinuation Symptom Checklist-Modified Rickels (DSCMR), which is a 30-item, patient-rated scale that assesses symptoms during the previous day to identify potential drug withdrawal. Each item was rated on a 0-to-3 scale and entered, by the patient, daily over the course of 2 weeks in a hand-held device. Extensive site and patient training were conducted and compliance with data entry was monitored frequently. Compliance with the ePRO device was defined as having a complete entry on each day.

Results: 103 patients were randomized in the 2-week, double-blind withdrawal phase with 98 patients completing the trial. Of the 103 randomized patients, the mean age was 42.74 years and the majority of patients were male (72.8%) with a baseline CGI-S score of 3.0. There was no statistically significant difference between treatment groups with respect to worsening of withdrawal symptoms as collected by the ePRO device. Compliance with the ePRO device was good with 72 of the 103 patients missing no more than 1 day and all patients adhered to the instructions by completing the ePRO for at least some portion of the 2 weeks

Conclusions: While noncompliance with PROs in schizophrenia is generally assumed, we have demonstrated good adherence and compliance to daily use of a hand-held ePRO device to assess symptoms in patients mildly to moderately ill with schizophrenia. Future research using an ePRO device in the collection of various outcomes in schizophrenia is warranted.

Learning Objectives:
- Describe the use of an ePro device in a multicenter schizophrenia clinical trial.
- Describe the outcomes of an ePRO device in a multicenter schizophrenia clinical trial.

Literature References:
- [FDA] Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.
- Rickels K., Espansa-Garcia F, Mandos L, et al. Physician Withdrawal Checklist. J Clin Psychopharmacol 2008;28:447–451.

PANEL SESSIONS
1:15 PM- 2:45PM
PANEL OVERVIEW:
NEW INSIGHTS ON PLACEBO RESPONSE IN ANTIDEPRESSANT TRIALS

Jonathan Rabinowitz, Ph.D.[1], Jonathan Rabinowitz, Ph.D.[1], Michael J. Detke, M.D., Ph.D.[2], Maurizio Fava, M.D.[3], Bruce Kinon, M.D.[4]
[1]Bar Ilan University, [2]MedAvante / Indiana University School of Medicine, [3]Massachusetts General Hospital, [4]Eli Lilly and Company

New data and insights on placebo response in antidepressant trials will be presented. This will be based on data from the following: (a) analyses of the NewMeds repository of patient level data on antidepressant drugs from Lilly, Astra Zenecca, Pfizer and Lundbeck, (b) data on therapeutic alliance and expectation bias and (c) data from various fields of medicine including studies of antidepressant drugs illustrating how manipulations of expectations through

knowledge (and certainty) of treatment have been found to have a significant effect on medication and placebo outcomes. Data to be presented show that differences in placebo-active treatment response relate to key demographic features of patients, that results could be obtained earlier and that therapeutic alliance and expectation bias can impair signal detection in antidepressant studies. Ways to incorporate these findings into designing more efficient trials will also be presented.

Learning Objectives:
- Learn about patient and study level variables that affect placebo response.
- Learn ways to minimize placebo response.

INDIVIDUAL ABSTRACT:
IMPROVING EFFICIENCY OF RCTS OF ANTIDEPRESSANT TRIALS: LESSONS LEARNED FROM THE NEWMEDS REPOSITORY OF RCT DATA FROM ASTRAZENECA, ELI LILLY, LUNDBECK, AND PFIZER
Jonathan Rabinowitz, Ph.D.
Bar Ilan University
Purpose: Present findings from NewMeds repository of antidepressant randomized controlled trial (RCT) data with a bearing on improving efficiency of trials.   There is considerable interest in improving the design of RCTs to more efficiently demonstrate treatment response in depression ([1](#), [2](#)).
Methodology: NEWMEDS repository includes anonymized patient level data from placebo-controlled trials of antidepressant drugs conducted by AstraZeneca, Eli Lilly, Lundbeck, and Pfizer (placebo, n=2549, active treatment, n=5504). Data from the Montgomery–Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD) were examined.
Results: Females showed significantly more drug-placebo differentiation than males: 14.33 (95% CI: 10.93-17.74) vs. 9.77 (95% CI: 6.40-13.14), respectively. Females on placebo (FP) improved least (28.9%), followed by males on placebo (MP) (32.9%), males on drug (MD) (42.7%) and the greatest improvement was in females on drug (FD) (43.2%). The percent of the total LOCF change at 6 weeks that was discernible at weeks 1 to 5 respectively was 19%, 43%, 60%, 85% and 93%. Data will also be presented on whether placebo vs. active treatment effects are more distinguishable in fixed vs. flexible dosing studies, under various admixtures of active treatment and placebo patients, with various numbers of study arms, when excluding sites with outlier placebo response, among patients with more severe illness, and for self-report vs. rater measures and in certain geographic regions.
The ways in which the results can be applied to designing for efficient future trials will be examined.

Learning Objectives:
- Participants will learn how trials could be designed more efficiently.

Literature References:
- Mallinckrodt CH, Tamura RN, Tanaka Y. Recent developments in improving signal detection and reducing placebo response in psychiatric clinical trials. J Psychiatr Res. 2011;45(9):1202-7.
- Tedeschini E, Fava M, Papakostas GI. Placebo-controlled, antidepressant clinical trials cannot be shortened to less than 4 weeks' duration: a pooled analysis of randomized

clinical trials employing a diagnostic odds ratio-based approach. J Clin Psychiatry. 2011;72(1):98-113.

INDIVIDUAL ABSTRACT:
THE ROLE OF EXPECTATIONS IN THE PLACEBO RESPONSE
Maurizio Fava, M.D.
Massachusetts General Hospital
Purpose: To illustrate how expectations affect placebo response in antidepressant trials and in other fields of medicine based on a meta-analysis of 146 MDD trials and a comprehensive review of the literature.

The issue of significant clinical improvement during treatment with placebo is particularly critical in central nervous system (CNS) drug trials, where excessive placebo responses have led to a significant reduction in the ability to detect a signal with compounds under development. A highly important contextual factor in placebo response is the expectation of benefit.

Results- In different conditions, manipulations of expectations through knowledge (and certainty) of treatment have been found to have a significant effect on medication and placebo outcomes. Numerous studies in post-operative oral surgical patients have shown that saline injections coupled with deceptive "knowledge" that patients were receiving morphine can produce an equivalent analgesic effect to morphine given by hidden infusion. For, example, recently, Amanzio, Benedetti et al. reported that the dose of analgesic medication needed to reduce post-operative pain by 50% were much higher with hidden infusions than with open infusions in which patients were given correct knowledge of what they were receiving. When the drugs were administered in a double-blind fashion, the effects were intermediate (i.e., between those of open-label and hidden). Along similar lines, open-label infusions of saline deceptively labeled "diazepam" produced an equivalent reduction in anxiety compared to diazepam given by hidden infusion. Studies in pain, Parkinson's disorder, and drug addiction have clearly shown that placebo response rates can be influenced by verbal cues that modulate patients' expectations. Further, recent studies have elucidated the neurobiology of placebo responses due to expectation. These experiments persuasively argue that manipulations of expectations through "knowledge" given to patients dramatically impacts outcomes. Moreover, in a recent meta-analysis by our group including 146 clinical trials on MDD, the placebo response was significantly higher (approximately 10% higher) when patients and clinicians were informed that the probability of receiving placebo was lower (between 20 and 33%) than the usual 50% chance. In the past decade, novel designs aimed at minimizing expectations have emerged, and there is some evidence that such approaches lead to lower placebo response rates. For example, our group has manipulated expectations in the first ever pilot randomized clinical trial (RCT) of open-label placebo in MDD and has found that the benefits of such treatment are extremely low under such low expectations. Finally, this presentation will provide an overview of possible methodological innovations that can help reduce placebo response rates through manipulation of expectations.

Learning Objectives:
- To understand how expectations affect the degree of placebo response in CNS clinical trials.
- To become familiar with novel study designs that manipulate expectations and reduce the overall placebo response.

Literature References:

- Papakostas, GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol.2009 Jan; 19(1): 34-40.
- Yang H, Cusin C, Fava M. Is there a placebo problem in antidepressant trials? Curr Top Med Chem. 2005;5(11):1077-86.

INDIVIDUAL ABSTRACT:
PLACEBO RESPONSE IN MAJOR DEPRESSIVE DISORDER TRIALS: THE PARTICULAR PROBLEMS OF THERAPEUTIC ALLIANCE AND EXPECTATION BIAS

Michael J. Detke, M.D., Ph.D.
MedAvante / Indiana University School of Medicine

Introduction: Bias in clinical trials may increase placebo response – and thus decrease signal detection. Therapeutic alliance and expectation bias are of particular concern in trials of CNS disorders such as Major Depressive Disorder (MDD) due to the subjective nature of key outcome measures. Therapeutic alliance may occur when clinicians and subjects form relationships that may (inadvertently) improve outcomes, such as through non-specific supportive psychotherapy, or a subject's reporting improvement to please the rater. Expectation bias can occur when an individual's expectations about an outcome influence their perceptions. Clinician expectation bias may occur if raters expect subjects to improve over time. Subject expectation bias may occur when subjects themselves expect to get better. Finally, rater and subject expectations may interact, with additive or synergistic effects.

Methods: We review studies of therapeutic alliance and expectation bias across multiple disease areas to assess how common they may be and to assess their impact on placebo response and signal detection. We examine the designs of these studies to identify methods for potentially mitigating expectation bias. We present new data from randomized clinical trials in related CNS disorders to examine the impact of these methods on signal detection (e.g., blinding to study visit number).

Results: Studies in several disease areas demonstrate that therapeutic alliance and expectation bias can increase placebo response and decrease signal detection. Several clinical study design features are relevant. Blinding raters to study visit number may reduce the expectation of improvement as treatment progresses. To achieve this it is necessary to use different raters across visits. Using multiple ratersalso reduces the likelihood of therapeutic alliance between raters and subjects. Three recent studies showed reduced placebo response or increased signal detection using different raters at consecutive visits.

Conclusions: Therapeutic alliance and expectation bias appear to be quite common. Using different raters across visits, and raters who are blinded to study visit number appears to yield decreased placebo response and better signal detection.

Learning Objectives:
- Understand how common expectation bias and therapeutic alliance are in clinical trials of MDD
- Understand how expectation bias and therapeutic alliance may increase placebo response and reduce signal detection in clinical trials of MDD
- Understand some methods for mitigating expectation bias and therapeutic alliance, such as the use of different clinician raters across trial visits, and blinding raters to visit number

Literature References:

- Kobak, KA et al. (2010). Site versus Centralized Raters in a Clinical Depression Trial: Impact on Patient Selection and Placebo Response. Journal of Clinical Psychopharmacology, 30 (2) 193-197
- Williams, JBW et al. (2010). Placebo Response Assessed by Site and Remote Blinded Centralized Raters in a GAD Trial. Presented at NCDEU Annual Meeting, Boca Raton, FL
- Shen, JHQ et al. (2011). A 6-week Randomized, Double-blind, Placebo-controlled, Comparator Referenced, Multicenter Trial of Vabicaserin in Subjects With Acute Exacerbation of Schizophrenia. Presented at ACNP annual meeting, Kona, Hawaii.

GENERAL DISCUSSION
Bruce Kinon, M.D.
Eli Lilly and Company

PANEL
1:15 PM – 2:45 PM
PANEL OVERVIEW:
PHARMACOGENETICS (AND PHARMACOGENOMICS) OF PSYCHOTROPIC DRUG RESPONSE

Anil K. Malhotra, M.D.[1], Kristin L. Bigos, Ph.D.[2], Thomas Laughren, M.D., Roy Perlis, M.D.. M.Sc.[3]
[1]The Zucker Hillside Hospital, [2]Lieber Institute for Brain Development, [3]Massachusetts General Hospital/HMS

Recent research indicates that pharmacogenetic and pharmacogenomic studies of antipsychotic drug response may be informative and there are now commercially available products to test specific genetic markers putatively associated with drug response. Nevertheless, the heterogeneity of drug response provides unique challenges for pharmacogenetics that may require novel approaches to fully realize the prospects for this area of inquiry. In this symposium, we will review the extant data on genetic approaches to drug response, and include academic, industry and regulatory considerations. Anil Malhotra (Zucker Hillside Hospital, NY) will first discuss genetic approaches to antipsychotic drug response, with a focus on the identification of variants that influence adverse events associated with treatment. He will present work from a genome-wide association study of drug-induced weight gain, and recent data on the utility of pharmacogenomic approaches towards the detection of genes for associated complex traits in the general population. Kristin Bigos (Lieber institute for Brain Development, MD) will present data on the key role of genetic variation in metabolic enzymes on the efficacy of antipsychotic drug treatment, including data from the large-scale CATIE trial, as well as work from drug treatment studies from her research group at the NIMH. These data highlight the importance of comprehensive assessment of genetic variation of pharmacokinetic factors, as well as pharmacodynamic factors in understanding drug response heterogeneity. David Collier (Eli Lilly, IN) will discuss academic work funded by the European Union on the role of genetic variation in prediction of clozapine-induced agranulocytosis, as well as provide a perspective in his role as an industry scientist focused on the use of molecular genetics to enhance drug discovery. Finally, Thomas Laughren will provide his view on the regulatory challenges facing pharmacogenetic testing of psychotropic drugs, an area of emerging interest as commercial applications begin to be considered within the biotechnology and pharmaceutical industry.

Finally, Roy Perlis (MGH, MA) will serve as discussant and highlight areas of confluence and discrepancy from the various perspectives presented during the symposium, in order to fully synthesize the wealth of data in this developing field.

Learning Objectives:
- To review the latest develoments in the pharmacogenetics of psychotropic drug response
- To discuss the role of pharmacogenetics from an academic, industry, and regulatory perspective.

INDIVIDUAL ABSTRACT:
PHARMACOGENOMIC APPROACHES TO DRUG-INDUCED ADVERSE EVENTS
Anil K. Malhotra, M.D.
The Zucker Hillside Hospital

Weight gain and related metabolic abnormalities are a significant side effect associated with antipsychotic drug treatment. Treatment studies comprised of chronic patients may underestimate the severity of this side effect, as prior treatments may have caused weight gain and obscure the true weight liability of the current drug treatment. Previously (Correll et al. 2009, JAMA), we showed that pediatric patients without prior exposure to antipsychotic medications experienced marked weight gain at 12 weeks of treatment with each of the study drugs; the weight gain was far greater than reported for previously treated patients and the weight change was highly variable. Therefore, we have completed the first genome-wide association study of antipsychotic-induced weight gain in previously untreated patients. We comprehensively characterized a discovery cohort of antipsychotic-naïve pediatric patients undergoing clinical treatment with the second generation antipsychotic drugs. Subjects were confirmed to be receiving antipsychotic drug by plasma blood levels, and were weighed at baseline, 4, 8 and 12 weeks of treatment. DNA was collected via blood sample and genotyping conducted with the Illumina 1M OmniQuad platform. Regression analysis of weight at 12 weeks of treatment versus baseline was conducted using both additive and recessive models. Subsequently, we assessed three additional cohorts of subjects treated with second generation agents and genotyped SNPs implicated in the discovery cohort, as well as conducted a rare variant analysis of our discovery cohort focused on missense SNPs.Quantitative trait loci (QTL) analysis revealed a region of the genome near the melanocortin 4 receptor gene (MC4R) that significantly associated with antipsychotic induced weight gain. SNPs in this region were also associated with weight gain in the three additional cohorts, with the same allele relationships and effect sizes observed across all three cohorts. Rare variant analysis also revealed a relationship between an amino acid substitution in the PCSK1 gene, also located in the proopiomelanocortin (POMC) pathway, and significant weight gain.Our data provide convergent evidence that genes in the POMC pathway are associated with antipsychotic-induced weight gain. These results have implications for gene x environment studies, as well as potential clinical impact for patients beginning antipsychotic drug treatment.

Learning Objectives:
- Identify and recognize the risk /benefit ratio of medications to treat alcohol dependence in patients with schizophrenia and other psychotic disorders.
- Increase awareness of the potential risk/benefit ratio of second generation anitpsychotics as a treatmtent for subject use in patients with schizophrenia and other psychotic disorders

INDIVIDUAL ABSTRACT:
GENETIC PREDICTORS OF ANTIPSYCHOTIC PHARMACOKINETICS AND PHARMACODYNAMICS

Kristin L. Bigos, Ph.D.
Lieber Institute for Brain Development

Antipsychotics have a high rate of discontinuation due to inefficacy and/or adverse effects. An ancillary study to the CATIE trials aimed to identify and quantify sources of variability in the clearance of antipsychotics. We have previously shown that sex and smoking are associated with differential clearance of several antipsychotics (Bigos et al. *J Clin Pharmacol* 2008;48(2):157-165). We are currently using pharmacokinetic and genetic data from the CATIE schizophrenia trial to identify genetic predictors of antipsychotic pharmacokinetics using non-linear mixed effects modeling

A candidate gene approach has identified several genetic variants in cytochrome P450 genes that highly predict the clearance of antipsychotics. We have shown that CYP3A43 significantly predicts clearance of olanzapine (Bigos et al. *Molecular Psychiatry* 2011; 16:620-625). We have recently found that the same SNP in CYP3A43 also significantly predicts 30% of risperidone clearance. Of the 230 SNPs in CYP450s, the CYP3A43 SNP (rs472660) was the most significantly associated with both risperidone and olanzapine clearance, and predicted most and the entire previous race effects in drug clearance, respectively. African Americans have a greater proportion of carriers of the fast metabolizing allele. This CYP3A43 SNP did not predict either quetiapine or ziprasidone, which was predicted based on the lack of racial effects on their clearance. The most significant predictors of ziprasidone and quetiapine clearance were SNPs located in the CYP2A/2B families of genes on chromosome 12. SNPs in other CYP gene families were also associated with clearance of one or more of the antipsychotics.

We are also conducting a GWA study using the original CATIE Affy 500K chip, and we have identified novel genetic predictors, which have not previously been associated with drug metabolism, including ST6GAL1 which best predicts olanzapine clearance. A long-term goal is to use these genetic variants to build models of predictors of antipsychotic drug metabolism in order to guide dosing. A separate goal is to use the variability in antipsychotic clearance as a covariate in studies designed to identify genetic predictors of antipsychotic drug response. We have shown that patients with schizophrenia who carry the risk allele for KCNH2, are 5-times less likely to discontinue olanzapine, only after controlling for differences in olanzapine clearance (Apud et al. *Am J Psychiatry.* 2012;169:725-734). The overall goal of this research is to use genetics to identify and characterize sources of variability in pharmacokinetics and response to psychotropics in order to optimize treatment strategies.

Learning Objectives:

- To be able to identify genes that predict differences in the pharmacokinetics of antipsychotics.

INDIVIDUAL ABSTRACT:
REGULATORY CONSIDERATIONS IN THE ROLE OF PHARMACOGENETIC MARKERS IN PSYCHIATRIC DRUG DEVELOPMENT

Thomas Laughren, M.D.

This talk will focus on practical regulatory issues that must be addressed in considering the use of pharmacogenetic markers in psychiatric drug development and the incorporation of information based on such markers into drug labeling. Pharmacogenetic markers could help in

identifying subgroups on the basis of either exposure to drug or dynamic response to drug. In either case, such information could be helpful in improving efficiency in evaluating either efficacy or safety of the new drug. Examples will be provided where pharmacogenetic markers have already had an impact on differentiating patients treated with psychiatric drugs on the basis of pharmacokinetics, i.e., exposure. Pharmacogenetic markers will also hopefully permit the subgrouping of heterogeneous populations into responsive and nonresponsive subpopulations. Accomplishing such a goal will necessitate careful pilot work and then hypothesis testing in definitive trials that demonstrate and replicate differential efficacy. Ideally a promising pharmacogenetic marker is identified in advance of the definitive phase 3 trials for a new drug, an assay is available for genotyping all patients prior to randomization, stratified randomization is accomplished, and a well-defined hypothesis strategy is established. In reality, establishing a pharmacogenetic marker often occurs in parallel with drug development, and flexibility is needed in applying these principles. Pharmacogenetic markers might also be useful in differentiating populations regarding vulnerability to certain adverse reactions, and a more exploratory approach to evaluating data is generally considered acceptable from a regulatory standpoint. Examples will be provided of how these principles can be practically applied in drug development. Biomarkers demonstrated to be useful could be permitted into labeling, providing that practical methods are available for identifying relevant patient subgroups. Such identification may necessitate co-development of devices, e.g., diagnostic kits, for testing patients in clinical practice.

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

Literature References:
- Woodcock J and Lesko LJ: Pharmacogenetics—tailoring treatment for outliers. NEJM 2009; 360(8):811-813.
- de Leon J: Pharmacogenomics: The promise of personalized medicine for CNS disorders. Neuropsychopharmacology Reviews 2009; 34:159-172.

GENERAL DISCUSSION
Roy Perlis, M.D., M.Sc.
Massachusetts General Hospital/HMS

PANEL
1:15 PM – 2:45 PM
PANEL OVERVIEW:
REVIVING DRUG DEVELOPMENT PARADIGMS FOR CNS DISORDERS

Charles Bowden, M.D.[1], Trevor Young, M.D., Ph.D., FRCP(C)[2], Eduard Vieta, M.D., Ph.D.[3], Steven Romano, M.D.[4], De-Maw Chuang, Ph.D.[5]
[1]University of Texas Health Science Center, San Antonio, [2]University of Toronto, [3]Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, [4]Pfizer, Inc., [5]National Institute of Mental Health, National Institutes of Health

This panel aims to address systemic hindrances that currently impede development of novel molecules and their efficient testing to yield innovative treatments that could contribute to

transformative treatments for the spectrum of disorders based in the Central Nervous System. Psychopharmacological approaches to drug discovery and clinical testing remain largely embedded in the same paradigms of half a century past. Current clinical trial methodologies contribute barriers to fundamental advances founded in translational research studies. Design features applied in maintenance phase registration studies of new drugs for mood and psychotic disorders have inherent weaknesses, e.g., high rates of missingness, that limit their external validity and generalizability. Panelists will systematically address these issues, focusing on alternative basic and translational research and innovative clinical research methods.

Signal transduction pathways provide scientists the means both to elucidate pathophysiology of diseases and develop and test in laboratory settings ways that existing treatments and new molecules which have the same molecular targets alter neuroplasticity and cellular resistance. Fortuitously, two primary mood stabilizers, valproate and lithium, have overlapping impacts, increasing histone acetylation, GSK3β phosphorylation and β Catenin, upregulating Bcl-2 and modulating intracellular calcium homeostasis. Panelists will link these translational approaches to a new statistical methodology; Multistate Outcome Analysis of Treatments (MOAT) that provides an alternative to traditional Kaplan Meier techniques. MOAT allows clinical states to be entered multiple times. It reports partitioned time in discrete, aggregated clinical states and allows for incorporation of indices of function or adverse effects. MOAT may allow shorter maintenance studies for registration purposes, since a substantially higher proportion of subjects will reach planned study endpoint, thereby increasing power. A second methodological innovation, Sequential Multiple Assignment Randomized Treatment (SMART) design will be reviewed. Challenges to pharmaceutical companies' implementation of these innovations, e.g., duration of exclusivity to amortize expenses, shifting from traditional clinical trial designs, data sharing, and fostering personalized medicine conclude the panel. We demonstrate the application and novel features of MOAT as applied to registration studies of two maintenance treatments for bipolar disorder. One important objective of the panel is to provide a feasible path that pharmaceutical companies, academic investigators, and national research facilities can consider to move beyond the small spectrum of drug categories currently in use.

Learning Objectives:
- Recognize the novel mechanisms for impacting CNS function provided by histone deacetylase inhibitors and alpha2 delta calcium channel modulators.
- Recognize the benefits that can accrue through moving beyond single point in time Kaplan Meier statistical designs in longer term clinical trials.

INDIVIDUAL ABSTRACT:
THERAPEUTIC POTENTIAL OF MOOD STABILIZERS IN MULTIPLE BRAIN DISORDERS: INSIGHTS FROM PRECLINICAL STUDIES
De-Maw Chuang, Ph.D.
National Institute of Mental Health, National Institutes of Health
The mood stabilizers lithium and valproic acid (VPA) are traditionally used in the treatment of bipolar disorder. However, their therapeutic mechanisms and the etiology of the disease remain elusive. The neuroprotective properties of both drugs continue to mount. Lithium and VPA, by inhibition of glycogen synthase kinase-3 and histone deacetylases, respectively, activate transcription and induce the expression of numerous neuroprotective and neurotrophic proteins including Bcl-2, heat shock protein 70, brain-derived neurotrophic factor and vascular

endothelial growth factor. Both drugs have been shown to protect against diverse insults, notably glutamate-induced excitotoxicity, by multiple mechanisms in cultured cells. In a rodent cerebral ischemia model of stroke, post-insult treatment with either lithium or VPA reduces brain infarction and blood-brain barrier breakdown, exerts anti-apoptotic and anti-inflammatory effects, stimulates neurogenesis and angiogenesis, and improves behavioral performance. In mouse traumatic brain injury (TBI), post-insult lithium treatment decreased TBI-induced brain lesion volume, neuroinflammation, neurodegeneration, anxiety-like behaviors, and memory impairment. These drugs also demonstrate remarkable benefits in a variety of other models of CNS disorders. Furthermore, co-treatment with lithium and VPA produces additive or even synergistic neuroprotective effects in some experimental settings, such as glutamate excitotoxicity and stem cell migration *in vitro*, and transgenic mouse models of Huntington's disease and amyotrophic lateral sclerosis *in vivo*. Together, these findings pave the way for future clinical investigation of innovative uses of mood stabilizers both in bipolar disorder and other CNS disorders.

Learning Objectives:
- Participants will be able to discuss the epidemiology, clinical manifestations, course and outcome of drug-induced catatonia
- Participants will be able to discuss the impact of second generation antipsychotic drugs on the incidence and phenomenology of catatonia in the context of psychosis

Literature References:
- Chiu C-T, Wang Z, Hunsberger JG and Chuang D-M: Therapeutic Potential of Mood Stabilizers Lithium and Valproic Acid: Beyond Bipolar Disorder. Pharmacological Reviews (in press).
- Chuang D-M, Leng Y, Marinova Z, Kim HJ and Chiu C-T: Multiple Roles of HDAC Inhibition in Neurodegenerative Conditions. Trends in Neurosciences 32: 591-601, 2009.

INDIVIDUAL ABSTRACT:
REFINING THE INTRACELLULAR TARGETS FOR MOOD STABILIZERS: A JOURNEY FROM THE SYNAPSE TO THE MITOCHONDRIA AND BACK AGAIN
Trevor Young, M.D., Ph.D., FRCP(C)
University of Toronto
While monoaminergic theories have been critical to our understanding of psychiatric illness and have a long tradition in shaping drug development for mood disorders, the past decade of work has focused attention inside the cell. Multiple intracellular targets, particularly in signal transduction pathways are robust targets for lithium and in some instances valproate. These include the phosphoinositide pathway, adenylyl cyclase and more specifically glycogen synthase kinase 3. This work shifts attention from the synapse to intracellular systems that also provide opportunities for novel drug development. These systems interrelate with mitochondrial targets ranging from BCL-2 to more fundamental components of this organelle such as the electron transport chain (ETC). Whereas BCL-2 relates directly to cell survival, discussed in the next session in the panel, a growing body of evidence has indicates multiple markers of decreased energy metabolism through the ETC and subsequent increased oxidative damage to proteins as targets of lithium. Studies in patients using converging methodologies ranging from brain imaging to blood cells and postmortem brain indicate oxidative damage in bipolar disorder. The consistency of findings of increased oxidative stress in patients and antioxidant effects of mood stabilizers provides one path for drug discovery. Antioxidants are receiving intensive study for

their mood stabilizing properties. Ironically, in the search for specific targets of oxidative damage in tissue from patients with bipolar disorder, the data return us to the synapse, with evidence of alterations in synaptic proteins such as SNAP-25 as well as oxidative damage and nitration in brain tissue from patients with bipolar disorder. As has been accomplished in other neuropsychiatric disorders in which specific targets of oxidative damage have been discovered, the potential for a detailed description of the molecular basis of bipolar disorder is stronger than ever. These data are well placed to influence development of new molecules for therapeutic interventions.

Learning Objectives:
- Recognize the challenges of drug development for major psychiatric conditions where there is as yet limited elaboration of underlying biology. In particular, recognize the value of robust translational research in support of rational drug development.
- Recognize the need for more advanced clinical trial methodology to enhance the probability of success in large, regulatory-intent Phase 3 clinical trials.

Literature References:
- Andreazza, AC et al. Mitochondrial complex 1 activity and oxidative damage to mitochondrial proteins in the prefrontal cortext of patients with bipolar disorder. Arch Gen Psychiatry 2010,67:360-368
- Anglin, RE et al. The psychiatric manifestations of mitochondrial disorders: a case adn review of the literature. J Clin Psychiatry 2012,73:506-512

INDIVIDUAL ABSTRACT:
BRIDGING TRANSLATIONAL AND CLINICAL RESEARCH STRATEGIES
Steven Romano, M.D.
Pfizer, Inc

Neuropsychiatric conditions contribute to significant and often chronic morbidity and extract a tremendous economic toll. The burden of disease of neuropsychiatric conditions, as measured in disability-adjusted life years (DALY, reflecting lost due to ill health, disability or early death), is 2-3x that associated with several other important disease areas, including cardiovascular, malignant neoplasms and respiratory diseases. Though the field has effective pharmacotherapies for some major neuropsychiatric conditions, including schizophrenia, major depression, bipolar disorder and Alzheimer's disease, most interventions are associated with small to modest effect sizes and insufficient response durability, and a significant proportion of patients remain symptomatic or at risk for episodic recurrence. Contributing to the challenge of developing more effective drug therapies is the complexity of the target organ and the existence of the blood-brain barrier, insufficient understanding of the underlying biology of most major psychiatric conditions, limited validated molecular targets and the absence of predictive and disease-specific animal models (with traditional animal models more appropriately described as screening "tools" for compounds of similar mechanism to currently available agents). Additionally, most of the clinical trials for major psychiatric conditions rely on subjective endpoints, and trial methodology in general has not reached a degree of refinement to adequately manage a tremendous degree of clinical heterogeneity and variability in experimental conditions. Fortunately, neuroscience as a field is evolving and our understanding of basic biology and the elaboration of relevant neurocircuitry, combined with major technological advances and enhanced clinical trial methodologies, should lead to the development of more effective and precise therapeutic interventions.

Learning Objectives:
- Recognize the challenges of drug development for major psychiatric conditions where there is as yet limited elaboration of underlying biology. In particular, recognize the value of robust translational research in support of rational drug development.
- Recognize the need for more advanced clinical trial methodology to enhance the probability of success in large, regulatory-intent Phase 3 clinical trials.

Literature References:
GENERAL DISCUSSION
Eduard Vieta, M.D., Ph.D.
Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM

PANEL
1:15 PM – 2:45 PM
PANEL OVERVIEW:
SCHIZOPHRENIA AND CO-OCCURRING SUBSTANCE USE DISORDERS:
EXPLORING COMMON NEUROCIRCUITS AND EFFECTIVE TREATMENTS:
NIAAA PANEL SESSION
Raye Z. Litten, III, Ph.D.[1], Alan Ivan. Green, M.D.[2], Andrew Chambers, Addiction Psychiatry[3], Ismene Petrakis, M.D.[4]
[1]NIAAA, [2]Geisel School of Medicine at Dartmouth, [3]Indiana University School of Medicine, [4]Yale University School of Medicine

Half of the patients with schizophrenia also have a co-occurring substance use disorders, involving alcohol, cannabis, and nicotine. The co-occurrence of substance use disorders with schizophrenia is associated with worse outcomes, including increased psychotic symptoms, medication noncompliance, increased hospitalization, and elevated social maladjustments, as compared to those patients without a co-occurring substance use disorder. It has been postulated that patients with schizophrenia have an increased vulnerability to addiction, due to a dysfunctional brain reward system involving the prefrontal cortical-ventral striatal circuits. Dr. Andrew Chambers will explore this hypothesis by testing the effects of alcohol, nicotine and cocaine in a rodent model of schizophrenia – the neonatal ventral hypocampal lesion (NVHL) model. Dr. Alan Green will translate this reward deficit hypothesis into human studies using brain imaging techniques. Moreover, his research has demonstrated that the atypical antipsychotic clozapine appears to be effective in reducing alcohol and cannabis use in these patients. Animal and human studies suggest that the effects of clozapine may be related to its weak dopamine D2 receptor blockade and elevated noradrenergic activity. Finally, Dr. Ismene Petrakis will explore different strategies for treating this comorbid population. These include testing medications approved for treating alcohol use disorders; medications that treat psychiatric disorders that may be particularly effective in addressing a comorbid substance use disorder; and medications that target potential common brain sites between the two disorders. Studies such as those discussed in this panel session are vital if we are to develop effective guidelines to help clinicians provide optimal treatment for this understudied population.

Learning Objectives:
- learn the latest treatment strategies for treating patients with schizophrenia and a co-occurring substance use disorders
- learn the latest theory on a common brain targets for both schizophrenia and substance use disorders

INDIVIDUAL ABSTRACT:
NEUROCIRCUITRY OF ADDICTION VULNERABILITY IN MENTAL ILLNESS

Andrew Chambers, Addiction Psychiatry
Indiana University School of Medicine

Addictions comorbidity is typical in patients suffering with schizophrenia and other major mental illnesses and is associated with detrimental psychiatric, medical, financial, legal, and mortality outcomes. Moving beyond self-medication explanations for dual diagnoses, which ultimately rely on, and promote the idea that addictive drugs are in some way therapeutic for mental illness, our lab has pursued evidence that the neuropathological substrates of mental illness involuntarily accentuate addition vulnerability. An over view of work conducted by our lab suggests that developmental abnormalities within temporal limbic structures inherent to the neurobiology of mental illness, change the structure and functionality of prefrontal cortical-ventral striatal circuits where drug reinforcement primarily occurs, fueling the fire of addictive disease. Using a neurodevelopmental animal model of schizophrenia as a preclinical tool for testing this theory, we provide supporting evidence with respect to different addictive drug types including cocaine, nicotine and alcohol, and in terms of new findings demonstrating how mental illness and addictive drug effects converge and integrate within prefrontal-cortical-striatal circuits. By defining a more unified nature of mental illness and addictive disease than has previously been recognized, this line of neuroscience has broad translational implications suggesting a need for greater integration of the addictions and mental health fields spanning clinical research, professional training, and clinical care missions.

Learning Objectives:
- Understand neuroanatomy and mechanisms underlying enhanced vulnerability to addictions in mental illness.
- Appreciate the translational implications of an integrative neuroscience of dual diagnosis

Literature References:
- Chambers, RA, Krystal, JH, Self, DW. (2001) "A neurobiological basis for substance abuse comorbidity in schizophrenia" Biological Psychiatry, 50:2: 71-83. PubMed PMID: 11526998; PubMed Central PMCID: PMC2913410.
- Chambers, RA, Sentir, AM, Conroy, SK, Truitt, WA, Shekhar, A (2010) "Cortical-striatal integration of cocaine history and prefrontal dysfunction in animal modeling of dual diagnosis" Biological Psychiatry, 67, 788-792. . Epub 2009 Oct 31. PubMed PMID: 19880093; PubMed Central PMCID: PMC2849854

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

Alan Ivan. Green, M.D.
Geisel School of Medicine at Dartmouth

Substance use disorder (especially involving alcohol or cannabis) occurs commonly in patients with schizophrenia and worsens their overall outcome. Treatment approaches that limit co-occurring substance use in these patients are limited. Most antipsychotic medications tested do not limit such substance use. Retrospective, open label, and recent small N randomized trials by our group and others all suggest, however, that the atypical antipsychotic medication clozapine does, in fact, limit both alcohol and cannabis use in these patients. Unfortunately, the side

effects of clozapine have severely restricted its clinical use. We have proposed that a dysfunctional dopamine mediated brain reward circuit in patients with schizophrenia may underlie their substance use, and, further, that substance use may ameliorate this dysfunction while also worsening symptoms of schizophrenia. Moreover, we have further proposed that clozapine, through its weak dopamine D2 receptor blockade, coupled with its effects on the noradrenergic system, may also tend to ameliorate this brain reward circuit dysfunction. Studies of resting state connectivity with fMRI, as well as task-based fMRI, in patients with schizophrenia and co-occurring cannabis use disorder are consistent with the reward dysfunction hypothesis in these patients. Moreover, pilot data suggest that cannabis may modulate this dysfunction. In studies of alcohol-drinking rodents, use of medication combinations to mimic the pharmacological action of clozapine suggest possible pathways toward development of new treatments for schizophrenia that may limit their substance use. Data from these animal and human studies will be presented, which taken together, provide intriguing clues about the basis of co-occurring substance use disorder in patients with schizophrenia and possible pathways toward developing effective treatments.

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

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

INDIVIDUAL ABSTRACT:
SCHIZOPHRENIA AND CO-OCCURRING SUBSTANCE USE DISORDERS: EXPLORING COMMON NEUROCIRCUITS AND EFFECTIVE TREATMENTS: NIAAA PANEL SESSION
Ismene Petrakis, M.D.
Yale University School of Medicine
Alcohol misuse in patients with schizophrenia is associated with significant psychiatric, medical and social consequences. Several strategies for treating these patients is possible 1) use of medications approved to treat alcohol use disorders 2) use of medications to treat the underlying psychiatric disorder that may be particularly effective in addressing a comorbid substance use disorder or 3) novel medications that target a potentially common neurobiology. Several studies (from our group and others), which have suggested that the medications to treat alcohol abuse are safe and have some efficacy, will be presented. Using administrative data, we have examined whether the second-generation antipsychotics are associated with a decrease in substance use compared to the conventional antipsychotics. Data from the VA nationally and data from the CATIE study will be presented. Finally, data from a pilot study using glycine to treat both the negative symptoms of schizophrenia and substance use will be presented. Future directions of other potential novel compounds will also be discussed.

Learning Objectives:
- Identify and recognize the risk /benefit ratio of medications to treat alcohol dependence in patients with schizophrenia and other psychotic disorders.
- Increase awareness of the potential risk/benefit ratio of second generation anitpsychotics as a treatment for subject use in patients with schizophrenia and other psychotic disorders

Literature References:
- Petrakis IL, Nich C, Ralevski E. Psychotic Spectrum Disorders and Alcohol Abuse: A Review of Pharmacotherapeutic Strategies and A Report on the Effectiveness of Naltrexone and Disulfiram. Schizophrenia Bulletin, 2006; 32(4):644-654.
- Kerfoot KE, Rosenheck RA, Petrakis IL, Swartz MS, Keefe RSE, McEvoy JP, Stroup TS, for the CATIE Investigators. Substance use and schizophrenia: Adverse correlates in the CATIE study sample. Schizophrenia Research, 2011; (132):177-82.

GENERAL DISCUSSION
Raye Z. Litten, III, Ph.D.
NIAAA

WORKSHOP
3:00 PM – 6:00 PM
WORKSHOP OVERVIEW:
CLINICALLY RELEVANT OR NOT? TREATMENTS FOR BIPOLAR DEPRESSION
Leslie Citrome, M.D., MPH[1], Terence A. Ketter, M.D.[2], Joseph R. Calabrese, M.D.[3], Mark A. Frye, M.D.[4]
[1]New York Medical College, [2]Stanford University School of Medicine, [3]University Hospitals Case Medical Center, [4]Mayo Clinic

In the course of their illness, persons with bipolar disorder can spend at least three-fold more time depressed than manic. In the US there are 10 FDA-approved treatments for bipolar mania, including lithium, valproate, carbamazepine, and a myriad of different second-generation antipsychotics, but only two FDA-approved treatments for bipolar depression: quetiapine monotherapy and olanzapine-fluoxetine combination. This imbalance of available treatment options cries out for new alternatives for bipolar depression that may be more efficacious, tolerable or both. This workshop is intended to provide a framework in which to assess clinical relevance for potentially new treatments for bipolar depression. After a brief overview of the differences between efficacy and effectiveness, and the measurements of number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH), the currently available options for bipolar depression are reviewed. This is followed by 2 presentations on treatment options in late-stage clinical development: monotherapy and adjunctive therapy with lurasidone, and adjunctive treatment with armodafinil. These new options possibly represent incremental advances to the current treatment armamentarium available for managing persons with bipolar depression. Additional issues relating to the appraisal of clinical trial evidence are then presented so that attendees can keep these in mind when additional data regarding these treatments become available.

Learning Objectives:
- To review the currently available options for the treatment of bipolar depression, using clinically relevant metrics.

- To appraise the evidence for the new treatments of bipolar depression that are presently in late stage of clinical development.

INDIVIDUAL ABSTRACT:
WHAT IS CLINICAL RELEVANCE AND CAN IT BE MEASURED?
Leslie Citrome, M.D., MPH
New York Medical College
Clinical trials can provide a large amount of data, some of it useful in day-to-day practice, some of it not. Clinicians often struggle to find interventions that make a difference in the wellbeing of patients. It is not always easy to discern whether or not a study result should actually change routine practice. Fortunately, there are tools available to help gauge clinical significance or clinical relevance. Clinicians can evaluate interventions by quantifying the balance between benefits [efficacy using number needed to treat (NNT)] and risks [tolerability as measured by number needed to harm (NNH)]. The applicability of trade-offs between benefits and risks will be largely influenced by what individual clinicians and patients view as being important and relevant. Personalized interpretation of NNT and NNH can facilitate efforts of clinicians and patients to balance benefits and risks in selecting optimal interventions. In addition, likelihood to be helped or harmed (LHH) can help quantify these trade-offs. An important caveat is that the generalizability of NNT and NNH calculated from registration efficacy studies to the "real world" is limited, as participants in controlled trials may have lower rates of comorbidities and less severe course of illness and less complex pharmacotherapy compared to patients in clinical settings. Effectiveness trials may provide additional information about treatment choices for patients who have complex illness, characterized by the need for multiple medications, and the presence of both psychiatric and somatic comorbidities

Learning Objectives:
- To be able to calculate number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH)

Literature References:
- Citrome L. Compelling or irrelevant? Using number needed to treat can help decide. Acta Psychiatr Scand. 2008 Jun;117(6):412-9.
- Ketter TA, Citrome L, Wang PW, Culver JL, Srivastava S. Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions? Acta Psychiatr Scand. 2011 Mar;123(3):175-89.
- Citrome L, Ketter TA. Teaching the philosophy and tools of evidence-based medicine: misunderstandings and solutions. Int J Clin Pract. 2009 Mar;63(3):353-9. Citrome L. Relative vs. absolute measures of benefit and risk: what's the difference? Acta Psychiatr Scand. 2010 Feb;121(2):94-102.

INDIVIDUAL ABSTRACT:
CURRENT LANDSCAPE FOR THE TREATMENT OF BIPOLAR DEPRESSION
Terence A. Ketter, M.D.
Stanford University School of Medicine
Background: The US Food and Drug Administration (US FDA) has approved only 2 treatments for acute bipolar depression (quetiapine monotherapy; olanzapine plus fluoxetine combination). These interventions both involve administration of a second-generation antipsychotic and thus are as likely to yield side effects (sedation/weight gain) as they are likely to yield response.

Hence, although these interventions may be preferable for patients more concerned about inefficacy compared to intolerability risks, other (as yet unapproved) interventions may be preferable for other patients more concerned about intolerability compared to inefficacy risks. We compared the therapeutic and adverse effects of these approved treatments and two important unapproved options (lamotrigine and antidepressants) for acute bipolar depression to inform clinical decision making.

Methods: Using data from large, randomized, double-blind, placebo-controlled acute bipolar depression trials and from a recent 6-study, 1,469-patient meta-analyses of double-blind, placebo-controlled antidepressants (68% adjunctive to mood stabilizers) in acute bipolar depression trials, we assessed number needed to treat (NNT) for response, number needed to harm (NNH) for sedation/weight gain and treatment-emergent affective switch/treatment discontinuation, and likelihood to help or harm (LHH = NNH / NNT) compared with placebo.

Results: For acute bipolar depression, lamotrigine compared with US FDA-approved treatments yielded substantively less sedation (NNH, 42 vs 6 -12), weight gain (NNH, -34 vs 6-19), and efficacy (NNT, 12 vs 4-6), but still more favorable efficacy:sedation likelihood (LHH, 3.5) than quetiapine (LHH, 1.0) and efficacy:weight gain likelihood (LHH, -2.8) than the olanzapine plus fluoxetine combination (LHH, 1.5). In a recent meta-analysis, antidepressants compared to placebo in acute bipolar depression yielded poor efficacy (NNT 36), but carried little risk of treatment-emergent affective switch (NNH 209) or treatment discontinuation (NNH -25), and thus a favorable efficacy:treatment-emergent affective switch likelihood (LHH 5.8).

Conclusions: For acute bipolar depression, lamotrigine compared with US FDA-approved treatments yielded better tolerability but poorer efficacy. Antidepressants also yielded adequate tolerability, but even more modest efficacy. Thus, lamotrigine and antidepressants might be preferable in patients more concerned about intolerability compared to inefficacy risks (e.g. with milder episodes), whereas the US FDA-approved treatments might be preferable in patients more concerned about inefficacy compared to intolerability risks (e.g. with more severe episodes). There is a need for additional treatment options for acute bipolar depression that provide not only adequate efficacy (NNT < 10) but also adequate tolerability (NNH > 10).

Learning Objectives:
- To understand the differential tolerability of treatment options for bipolar depression

Literature References:
- Ketter TA, Citrome L, Wang PW, Culver JL, Srivastava S: Treatments for bipolar disorder: Can Number Needed To Treat/Harm help inform clinical decisions? Acta Psychiatr Scand 2011;123(3):175-89
- Srivastava S, Ketter TA. Clinical relevance of treatments for acute bipolar disorder: balancing therapeutic and adverse effects. Clin Ther 2011;33(12):B40-8

INDIVIDUAL ABSTRACT:
INCREMENTAL ADVANCES IN TOLERABILITY: THE CASE FOR LURASIDONE
Joseph R. Calabrese, M.D.
University Hospitals Case Medical Center
Lurasidone is an atypical antipsychotic agent belonging to the class of benzisothiazol derivatives which appears to possess novel pharmacodynamic properties. This compound exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors ($IC_{50} > 1,000$ nM), which may account for its apparent improved tolerability as reflected in its low rates excessive daytime fatigue, increased appetite, and weight gain. Its efficacy in bipolar I depression has been shown in a 6-

week monotherapy study and a 6-week adjunctive study during which included either lithium or valproate (currently under review by the FDA).

Although the mechanism of lurasidone's antipsychotic efficacy is unknown, it may be mediated by a combination of central D_2 and $5HT_{2A}$ receptor antagonism. The mechanism of lurasidone's efficacy in bipolar I depression is also unknown, but preclinical studies in animal models implicates the role $5\text{-}HT_7$ receptors in antidepressant and anxiolytic actions, cognition, learning, memory, sleep, and circadian rhythms. Based upon rat brain autoradiography studies using [^{3}H]SB-269970, a selective $5\text{-}HT_7$, it has been reported that the predominant distribution of $5\text{-}HT_7$ receptors in the limbic regions of the brain, including the septum, thalamus, hypothalamus, hippocampus, and amygdala. Lurasidone (10-1000 nM) concentration-dependently inhibited [^{3}H]SB-269970 binding in all of these brain regions as potently as the selective $5\text{-}HT_7$ receptor antagonist SB-656104-A, demonstrating that lurasidone has potent $5\text{-}HT_7$ receptor binding affinity (Hedlund et al 2009). In fact, lurasidone has an antidepressant-like action in the tail suspension and forced swim tests, animal models of depression (Hedlund et al 2011, ACNP meeting).

In contrast to an 8-week study of quetiapine monotherapy in bipolar I or II depression, which was accompanied a 26%, 16%, and 9% rates of drug discontinuation due to adverse events (quetiapine 600mg daily, 300mg daily, and placebo, respectively), the rates of drug discontinuation due to adverse events on lurasidone monotherapy were 6% 7%, and 6% (lurasidone 80-120mg daily, 2-60mg daily, and placebo, respectively). The rates of drug discontinuation due to adverse events when lurasidone was used adjunctively with either lithium or valproate were 6.0% vs. 7.9% (lurasidone 20-120mg, placebo, respectively); No acute studies of quetiapine were conducted that employed adjunctive designs.

Within the quetiapine monotherapy study, the overall rate of drug discontinuation was 54% on 600mg mg/day, 67% in the 300mg/day group, and 59% on placebo. Within the lurasidone monotherapy study, the overall rates of drug discontinuation were 27% on 80-120mg per day, 26% on 20-60mg per day, and 25% on placebo. Within the adjunctive lurasidone study, the overall rates of drug discontinuation were 21.9% within the adjunctive lurasidone group and 17.6% on placebo.

There exists need to compare the spectrum of efficacy and tolerability of lurasidone to quetiapine in double blind placebo-controlled studies sufficiently powered to contrast rates of adverse events and drug discontinuation.

Learning Objectives:
- Discontinuation due to adverse events

Literature References:
- Hedlund PB: The 5-HT7 receptor and disorders of the nervous system: an overview. Psychopharmacology 2009;206:345-354.
- Calabrese JR et al: A randomized, double-blind, placebo-controlled trial of quetiapine, in the treatment of bipolar I or II depression. Am J Psychiatry. 2005 July; 162(7):1351-1360.

INDIVIDUAL ABSTRACT:
INCREMENTAL ADVANCES IN EFFICACY: THE CASE FOR ADJUNCTIVE ARMODAFINIL
Mark A. Frye, M.D.
Mayo Clinic

Background: The objective of this study was to evaluate the efficacy and safety of armodafinil as an adjunctive therapy for major depression associated with bipolar I disorder.

Methods: Adult bipolar I patients currently on mood stabilizers and experiencing a major depressive episode (DSM-IV-TR) for 4 to 52 weeks, were randomized to receive adjunctive armodafinil 150 mg, 200 mg, or placebo. The primary outcome was the mean change from baseline to week 8 in the 30-Item Inventory of Depressive Symptomatology-Clinician-rated (IDS-C30) total score. Secondary outcomes included mean change at week 8 on IDS-C30 individual items, IDS-C30 response rate, Clinical Global Impression response and Global Assessment of Function (GAF). Safety assessments included adverse events (AEs), Young Mania Rating Scale (YMRS), Columbia Suicidality Rating Scale, Hamilton Anxiety Scale (HAM-A), and Insomnia Severity Index (ISI). Mixed-model repeated measures were utilized for the primary outcome measure with analysis of variance or Cochran-Mantel-Haenszel test for secondary outcome measures. Final visit data is from the last post-baseline assessment.

Results: 433 subjects were randomized (n=199 placebo, n=201 armodafinil 150 mg, n=33 armodafinil 200 mg). The 200-mg armodafinil group was discontinued based on previous findings of a lack of differential dose response between the 150- and 200-mg groups, and these patients were assessed for safety only. Baseline demographics and disease characteristics were comparable between the armodafinil 150-mg group and placebo group. There was a significantly greater decrease at week 8 for the armodafinil 150-mg group compared with placebo for mean IDS-C30 total score (–21.7 vs –17.9; p=0.0097) and at final visit for five IDS-C30 individual items: panic/phobic symptoms (p=0.0440), increased appetite (p=0.0096), concentration/decisions (p=0.014), energy/fatigability (p=0.0375), and leaden paralysis/physical energy (p<0.001). The IDS-C30 response rate was significantly greater in the armodafinil 150 mg group vs. placebo at week 8 (55% vs. 39%; p=0.0084) and final visit (46% vs. 34%; p=0.0147). The percentage of CGI-S responders and change in GAF were not significantly different between groups. Discontinuations due to AEs were 4% for placebo, 5% for armodafinil 150 mg, and 3% for armodafinil 200 mg. The most common AEs were headache, diarrhea, and nausea. YMRS, HAM-A, and ISI scores decreased from baseline to final visit in all groups. There was 1 suicide attempt in the placebo group and 2 reports of suicidal ideation in the armodafinil 150-mg group. The number needed to treat for armodafinil 150 mg vs. placebo = 9 with number needed to harm with regards to AE discontinuation=55.

Discussion: Armodafinil 150 mg significantly improved depressive symptoms compared with placebo in patients with bipolar I disorder when given as adjunctive treatment to mood stabilizers. Adjunctive armodafinil 150 mg compared with placebo was well tolerated, with no evidence for worsening symptoms of mania, suicidality, anxiety, insomnia, or other adverse events.

Learning Objectives:
- To increase understanding of the evidence base / clinical trial database for armodafinil in bipolar depression
- To increase understanding of side effect burden and tolerability for armodafinil

Literature References:
- 106. Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE, Althsuler LL, Leverich GL, Post RM. Modafinil in the treatment of bipolar depression: a placebo, controlled evaluation. Am J Psychiatry 2007;164:1242-1249

- 131. Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: A randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry. 2010;71:1363-1370

GENERAL DISCUSSION
Terence A. Ketter, M.D.
Stanford University School of Medicine

WORKSHOP
3:00 PM – 6:00 PM
WORKSHOP OVERVIEW:
CRITICAL ELEMENTS OF ADJUNCTIVE TRIAL DESIGN IN MDD
Craig Nelson, M.D.[1], Michael E. Thase, M.D.[2], Maurizio Fava, M.D.[3], Robert Berman, M.D.[4], Tiffany R. Farchione, M.D.[5]
[1]University of California San Francsico, [2]Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center, [3]Massachusetts General Hospital, [4]Bristol-Myers Squibb, [5]US Food & Drug Administration

Adjunctive or augmentation trials in major depressive disorder (MDD) have a long history dating to reports of L-tryptophan and stimulants in the 1960s. Early augmentation trials varied greatly in sample sizes, timing of augmentation, dosing and duration of augmentation, and treatment resistance of the sample, In the past decade three atypical agents-olanzapine, aripiprazole, and quetiapine have been approved by the FDA for use as adjunctive agents in MDD, or in the case of olanzapine for use with fluoxetine in treatment resistant depression. While the overall quality of adjunctive trials has improved, considerable variability remains.

In this workshop we will examine key issues relevant to adjunctive trial design. Michael Thase, M.D. will review the major design issues in recent adjunctive trials in MDD including definition of treatment resistance, length of initial antidepressant treatment, length of adjunctive treatment, methods of blinding the start of adjunctive treatment, and what to do with initial antidepressant responders. Craig Nelson, M.D. will examine the effect of level of response to the initial antidepressant or baseline severity on adjunctive treatment outcome. While this question was prompted by the clinical question of whether adjunctive treatment is primarily useful in partial responders, the findings suggest greater change may be seen in more severe patients and that it may be difficult to demonstrate efficacy in mild depression with residual symptoms. Maurizio Fava, M.D. will address the question of demonstrating efficacy for residual symptoms and in particular will discuss the use of scales designed to increase sensitivity for measurement of residual symptoms. Robert Berman, M.D. has firsthand experience as the director of the adjunctive aripiprazole program. He will discuss his perspective on operational aspects of those trials, study design choices and optimizing site performance. Finally Tiffany Farchione, M.D. from the FDA will join the group to give her perspective regarding key elements of adjunctive trial design. For example, how to define the sample--treatment resistant or suboptimal response—and what are the implications for labeling?

We anticipate that adjunctive treatment will be a "growth area" in depression and thus a workshop addressing issues in adjunctive trial design would be timely. In addition to encouraging discussion from the audience, at the conclusion of the presentation, the panel will attempt to reach consensus on the important elements of adjunctive trial design.

Learning Objectives:

- The participant will be able to describe the key elements in adjunctive trial design in MDD
- The participant will be able to recognize the role of baseline severity in the outcome of adjunctive trial design
- The particpant will be able to identify tools for assessment of residual symptoms.

INDIVIDUAL ABSTRACT:
ADJUNCTIVE THERAPIES TRIALS DESIGNS: BASICS AND UNANSWERED QUESTIONS

Michael E. Thase, M.D.
Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center

In an era in which essentially no mechanistically novel antidepressants have been introduced in the past decade, clinicans have attempted to address more difficult to treat cases of depression by greater use of combined and adjunctive strategies. For the purposes of this presentation, the term combined is used to describe two or more antidepressantsm whereas an adjunctive strategy describes the addition of a second medication that is not primarily considered an antidepressant. The terms adjunctive and augmentation therapies are also virtually synonymous, though the FDA prefers the former term.Although some adjunctive strategies have been used for decades (e.g., lithium and thyroid augmentation strategies), currently only three second generation antipsychotics - aripiprazole, quetiapine, and olanzapine (specifically in combination with fluoxetine) have been approved by the FDA as adjuncts to antidepressants. The pathway to regulatory approval has been relatively straightforward: at least two randomized controlled trials are needed in which patients who have not responded to a trial of antidepressant therapy show a significantly greater response to the adjunctive therapy as compared with a double blind placebo when added to ongoing antidepressant therapy. With respect to this basic question, the major design consideration involve:1) whether or not the index antidepressant trial is conducted prospectively and 2) whether the choice of antidepressants is narrow (as in olanzapine fluoxetine combination) or broad (i.e., most widely used antidepressants). Another important decision is whether or not the patients have simply shown an inadequate response to a trial of antidepressant therapy or meet a stricter definition of treatment resistant depression. Successful regulatory review has been achieved by companies taking both very restrictive and very inclusive approaches. Although the failure rate (i.e., drug is not significantly more effective than placebo) of adjunctive therapy trials has been relatively low with second generation antipsychotics, there have been a number of notable failures with other classes of therapies. Moreover, even when an adjunctive therapy program leads to approval, many important questions remain unanswered about relative efficacy, cost-effectiveness, benefit-risk, and the optimal duration of adjunctive therapy, For the SGAs, for example, the risks of tardive dyskinesia and metabolic complications have not yet been determined with any certainty. Until adequate post-marketing research programs are mounted to address these important topics, prudent clinicians have good reason to be cautious in their use of adjunctive therapies.

Learning Objectives:
- The participant will become familiar with the pros and cons of the basic research designs used to evaluate adjunctive therapies for depression
- The participant will be able to identify the critical questions not yet addressed by studies of adjunctive therapies

Literature References:
- Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, Turkoz I, Lasser RA, Loescher A, Bouhours P, Dunbar F, Nemeroff CB. Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology. 2006 Nov;31(11):2505-13.
- Berman RM, Thase ME, Trivedi MH, Hazel JA, Marler SV, McQuade RD, Carson W, Baker RA, Marcus RN. Long-term safety and tolerability of open-label aripiprazole augmentation of antidepressant therapy in major depressive disorder.

INDIVIDUAL ABSTRACT:
EFFECTS OF RESPONSE TO THE INITIAL ANTIDEPRESSANT ON ACUTE PHASE OUTCOME IN ADJUNCTIVE TREATMENT TRIALS

Craig Nelson, M.D.
University of California San Francsico

Use of adjunctive treatments in MDD has often been guided by practical considerations, such as partial response, rather than actual efficacy data. New evidence regarding the relationship of initial response to outcome with adjunctive treatment is informative for clinical decisions and trial design. The objective of this presentation will be to determine how the level of initial antidepressant response may influence adjunctive treatment outcome.

Data from 3 similar adjunctive aripiprazole trials were pooled and examined. Briefly patients with major depressive disorder (MDD) and 1-3 prior failed antidepressant trials entered an 8-week prospective trial with a SSRI or venlafaxine. Patients who failed to respond were blindly randomized to aripiprazole or placebo for 6 weeks. The MADRS was used to assess change. Two methods were used to define depression status at the time of randomization—level of improvement (partial or minimal) response and depression severity (mild, moderate, or severe).

A total of 1038 patients failed to respond to the prospective trial (minimal response N=746 and partial response N=292). Among the minimal responders, change scores and response and remission rates were significantly greater with aripiprazole than placebo. In partial responders the advantage of aripiprazole over placebo was significant at some time points but not at endpoint. It appeared that response and remission rates continued to improve appreciably on placebo suggesting ongoing effects of the initial antidepressant. An analysis based on MADRS severity at the time of randomization (mild N=415; moderate N=385; severe N=265) (unpublished data) found significant differences between drug and placebo on change scores in each group. In both treatment arms absolute change scores increased with severity. Alternatively remission rates dropped markedly as severity increased.

Severely depressed patients will show greater magnitude of change but substantially lower remission rates. Drug-placebo differences may or may not be affected. Partial responders are more likely to continue to show continued improvement on placebo and the initial antidepressant. Extrapolating from this data suggests that detecting differences in depression scores may be especially difficult in responding patients who have residual symptoms.

Learning Objectives:
- Describe the effect of minimal response on outcome
- Recognize the effects of baseline severity on change and remission

Literature References:

- Nelson JC, Thase ME, Bellocchio EE, et al. Efficacy of adjunctive aripiprazole in patients with major depressive disorder who showed minimal response to initial antidepressant therapy. Int Clin Psychopharmacol 2012;27(3):125-33.
- Nelson JC: Augmentation strategies in the treatment of major depressive disorder. Recent findings and current status of augmentation strategies. CNS Spectr 2007; 12:6–9

INDIVIDUAL ABSTRACT:
METHODOLOGICAL CHALLENGES IN CNS DRUG TRIALS TARGETING RESIDUAL SYMPTOMS IN DEPRESSION
Maurizio Fava, M.D.
Massachusetts General Hospital

A number of augmentation trials in major depressive disorder (MDD) have targeted residual symptoms and the results of these efforts have been relatively mixed. In particular, the design of these trials has been plagued by several major issues: 1) the problem of a "floor effect", that is the difficulty in detecting robust clinical changes in illness severity when the symptoms are very mild or subthreshold; 2) the problem of biased enrichment, that is the need to enrich the sample with patients who report the specific residual symptoms that are targeted by the treatment (in such cases, clinicians are biased to overestimate the severity of residual symptoms so that the patient is deemed appropriate for enrollment); 3) the problem of a delayed effect of the antidepressant therapy that gets augmented with either the experimental treatment or placebo, delay that may be more pronounced for difficult-to-treat patients and may confound the results of studies using lead-in, open-label treatment phases. Another set of issues is related to the issue of residual symptom measurement. Most of the scales that are used in depression trials were developed to study clinical changes in patients acutely/severely ill. Therefore, most depression scales do not discriminate well various degrees of mild, residual symptomatology. In addition, the heterogeneity of MDD leads to the presence of variable clusters of residual symptoms, such as anxiety, sleep disturbances, and fatigue. In some cases, troublesome residual symptoms are not even assessed by standard depression scales. For example, cognitive symptoms, such as diminished concentration and memory, are present in approximatley 30% to 40% of patients who have responded to standard antidepressant therapies, and certain augmentation strategies have shown the ability to improve such symptoms. However, these effects cannot be detected when more standard depression scales are used, and these scales do not capture well these cognitive symptoms. In addition, the relative absence of positive affect and well being is often considered an important residual symptom in MDD, and yet most of the MDD scales focus on symptoms and not on such aspects of the illness. All these methodological and design issues need to be tackled by investigators to make augmentation trials in MDD more informative. This presentation will review these issues and provide some examples of novel approaches aimed at addressing these problems in MDD augmentation trials.

Learning Objectives:
- To become familiar with the issues of measurement of residual symptoms in depression.

Literature References:
- Fava M. Pharmacological approaches to the treatment of residual symptoms. J Psychopharmacol. 2006 May;20(3 Suppl):29-34.
- Targum SD, Fava M. Fatigue as a residual symptom of depression. Innov Clin Neurosci. 2011 Oct;8(10):40-3.

INDIVIDUAL ABSTRACT:
INDUSTRY PERSPECTIVE: DEVELOPING TREATMENTS THAT GO BEYOND FIRST-LINE THERAPY IN MAJOR DEPRESSIVE DISORDER
Robert Berman, M.D.
Bristol-Myers Squibb

Significant unmet medical need for the treatment of Major Depressive Disorder (MDD) has driven decades of urgent research within academia and industry to find novel pharmacological treatments. That is, over 60% of patients do not achieve remission following conventional antidepressant treatment. Testing pharmacologic agents in depressed populations presents multiple challenges that have led to disappointing rates of failed trails even with established antidepressants. Why do trials in MDD fail so commonly? Suspected causes include issues related to maintaining rating quality, sensitivity of outcome scales, selection of appropriate patients, trial duration and placebo response. Despite significant consideration of these issues, the actual science of clinical trial methodology is generally limited to the assessment of case series (i.e., comparing failed and successful trials); it therefore lacks conclusiveness and can be prone to unsubstantiated trends. This presentation will discuss how new as well as forsaken hypotheses on trial methodology were incorporated into a program to assess the efficacy of adjunctive aripiprazole in the treatment of patients with MDD who had an inadequate response to prior treatment. The program of studies included novel design features intended to limit placebo response and reduce bias by sites, raters and patients. In addition, an intensive program was employed to enhance rating consistency. Best practices on sponsor engagement helped maintain site focus. The basis for selecting specific design features and operational approaches will be discussed.

Learning Objectives:
- To understand the differential tolerability of treatment options for bipolar depression

Literature References:
- Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007 Jun;68(6):843-53.
- Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, Trivedi MH, Thase ME, Berman RM. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2008 Jul;69(7):1046-56.
- Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, Carson WH, Adson D, Taylor L, Hazel J, Marcus RN. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009 Apr;14(4):197-206.

GENERAL DISCUSSION
Tiffany R. Farchione, M.D.
US Food & Drug Administration

WORKSHOP
3:00 PM – 6:00 PM
WORKSHOP OVERVIEW:
NEW ADVANCES IN CHILD PSYCHOPHARMACOLOGY

Benedetto Vitiello, M.D.[1], Adelaide S. Robb, M.D.[2], John T. Walkup, M.D.[3], Joseph C. Blader, Ph.D.[4]

[1]NIMH, [2]Children's National Medical Center, [3]Weill Cornell Medical College and New York-Presbyterian Hospital, [4]Stony Brook State University of New York

This panel will report and discuss new data from recently completed clinical trials of mood stabilizers and antipsychotics in children diagnosed with bipolar disorder, and will examine the effectiveness of interventions to prevent relapse and recurrence of unipolar depression in youth. The panel will include three data presentations. First, Dr. Adelaide Robb will present efficacy and safety data from recently completed randomized clinical trials in child bipolar disorder. Second, Dr. John Walkup will present the results of the augmentation and medication switching strata of the Treatment of Early Age Mania study (TEAM), a NIMH-funded 5-site randomized clinical trial of lithium, valproate, and risperidone, alone and in combination, in children with bipolar mania. Finally, Dr. Graham Emslie will present the result of a recently completed NIMH-funded trial to prevent relapse and recurrence in youths with major depression who have responded to antidepressant treatment. These presentations will be followed by a panel debate on promising research perspectives in pediatric psychopharmacology.

Learning Objectives:
- To provide new information on both the efficacy and safety of mood stabilizers and second generation antipsychotics in children
- To illustrate evidence-based strategies to improve the long-term outcome of adolescent depression by preventing relapse and recurrence.

INDIVIDUAL ABSTRACT:
WHAT IS THE CURRENT EVIDENCE OF THE EFFICACY AND SAFETY OF TREATMENTS FOR CHILDREN WITH BIPOLAR DISORDER?

Adelaide S. Robb, M.D.

Children's National Medical Center

Pediatric bipolar disorder affects up to 1% of youth. The rates of diagnosis have been increasing in the last 10 years as more research into diagnosis and treatment has taken place. In the last 10 years multiple large multisite trials have been completed for pediatric and adolescent bipolar disorder. This session will review recent medication trials for pediatric bipolar disorder. Two large federally funded trials CoLT (Collaborative Lithium Trial I and 2) and TEAM (Treatment of Early Age Mania) examined pediatric bipolar treatment with lithium and a comparison of lithium, valproic acid, and risperidone. A large industry funded trial of lamotrigine examined this medication as an add-on agent to youth on one or two standard mood stabilizers with persistent bipolar manic, mixed or depressed symptoms. Response was determined in an open label trial followed by blinded discontinuation. The CoLT 1 trial demonstrated the appropriate tolerable lithium titration schedule and rate of response with lithium. The CoLT 2 trial testing the effectiveness of lithium vs. placebo will complete data collection in the spring 2013. The TEAM study demonstrated that risperidone was superior to lithium and valproic acid in treatment naïve patients with bipolar disorder. Open label results from the lamotrigine study show that adding lamotrigine to other mood stabilizers improves mood symptoms in patients with manic, mixed and depressed mood states. Multiple medications have been found to be effective in the treatment of pediatric bipolar disorder, especially the atypical antipsychotics followed by lithium; valproate, effective or adults, has been the least effective. Despite this efficacy, many

children and adolescents with bipolar disorder may need more than monotherapy for optimal symptom control and minimization of adverse effects.

Learning Objectives:
- To learn of the most recent data on the efficacy and safety of mood stabilizers in children and adolescents with bipolar disorder.
- To understand the comparative benefit/risk balance of various pharmacological agents to treat youths with severe mood dysregulation.

Literature References:
- B Geller, JL Luby, P Joshi, KD Wagner, G Emslie, JT Walkup, DA Axelson, K Bolhofner, A Robb, DV Wolf, MA Riddle, B Birmaher, ND Ryan, J Severe, B Vitiello, RTillman, P Lavori. "Comparative Effectiveness of Risperidone, Lithium, and Valproate for Bipolar I Disorder, Manic or Mixed Phase, in Children and Adolescents: A Randomized Controlled Trial". Archives of General Psychiatry. Published online January 2, 2012.
- Dosing strategies for lithium monotherapy in children and adolescents with bipolar I disorder.Findling RL, Kafantaris V, Pavuluri M, McNamara NK, McClellan J, Frazier JA, Sikich L, Kowatch R, Lingler J, Faber J, Rowles BM, Clemons TE, Taylor-Zapata P.

INDIVIDUAL ABSTRACT:
A RANDOMIZED TRIAL OF AUGMENTING AND SWITCHING MEDICATIONS IN CHILD BIPOLAR DISORDER
John T. Walkup, M.D.
Weill Cornell Medical College and New York-Presbyterian Hospital
The first stratum of the Treatment of Early Age Mania (TEAM) study evaluated lithium, risperidone and valproate in children with bipolar I disorder who were antimanic medication naïve. We know report on the effectiveness of adding or switching medication for children who were partial or non-responders, respectively.

Methods: Participants (n=154) were children ages 6-15 (10.2 ± 2.7 yr) with DSM-IV bipolar I disorder (mixed or manic phase), either non-responders or partial responders to one of the three study medications. Non-responders were randomly assigned to one of the other two antimanic medications and cross-tapered. Partial responders were randomly assigned to one of two other antimanic medications as an add-on to their initial medication.

Results: Response rates for those participants who switched to risperidone (47.6%) were higher that than those who were switched to either lithium (12.8%; p=.005) or valproate (17.2%; p=.03); response rates for partial responders who added risperidone (53.3%) were higher than those who added on lithium (26.7%; p=.07) or valproate (0%; p=.0002). Risperidone treatment was associated with weight gain.

Conclusions: Risperidone was effective than lithium or valproate for patients with bipolar I disorder who were non- or partial-responders to an initial antimanic medication trial. Weight gain is an important complication of risperidone treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00057681.

Learning Objectives:
- To inform on how to treat children with manic symptoms who had not adequately improved on a previous therapeutic trial of mood stabilizer or risperidone
- To learn of the adverse effects of lithium, valproate and risperidone when used alone or in combination in children with mood disturbance.

Literature References:
- Geller et al., Arch Gen Psychiatry. 2012 May;69(5):515-28.

INDIVIDUAL ABSTRACT:
CHALLENGES AND REWARDS IN TRIALS TO EVALUATE TREATMENT STRATEGIES FOR PARTIAL RESPONDERS TO FIRST-LINE THERAPY
Joseph C. Blader, Ph.D.
Stony Brook State University of New York

Despite an emerging evidence base to guide psychopharmacotherapy for a number of child and adolescent disorders, treatment for youngsters who experience suboptimal response to initial therapy has a slender empirical foundation and, by necessity, remains largely improvisational in clinical practice. Widespread and growing use of polytherapy in this patient population underscores the unmet need for data that offer guidance on management for patients whose partial response to evidence-based monotherapy compels further intervention to reduce residual impairments. This workshop presentation will first identify issues important to the concept of 'partial response', which can designate diverse phenomena, including (1) only meager improvement in all major symptom areas, (2) marked improvement in some symptom domains but not others, or (3) impact on symptoms that vacillates over time. Such distinct manifestations of partial response have, in turn, strong implications for the second topic, trial design. Key design considerations for review include how one: (a) determines true refractoriness to first-line therapy, (b) insures that residual 'symptoms' are not in fact iatrogenic complications of current treatment, (c) selects a preferred strategy to assess (e.g., augmentation, supplantation, modification), (d) chooses appropriate and ethical comparator treatments, (e) estimates sample size requirements, recruitment needs, and the range of desirable effect sizes, and (f) identifies the critical endpoints and analyses. Although the tendency for such trials to involve more severely ill patients may be a disincentive to some investigators, the likelihood of diminished response to placebo or other comparators often improves the prospects for detecting a signal for treatments that truly confer benefits. Findings from two stepped-treatment trials with children and adolescents (for SSRI-refractory depression and for stimulant-refractory aggression with ADHD) will provide illustrative context for the discussion.

Learning Objectives:
- Participants will enhance their understanding of how to define partial response for childhood disorder and use that understanding to design trials that will best address the needs of the patient population of interest
- Attendees will gain familiarity with a "checklist" of factors to weigh in order to develop and evaluate trials for partial treatment responders that are valid, feasible, and have sufficient power.

Literature References:
- Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, Vitiello B, Ritz L, Iyengar S, Abebe K, Birmaher B, Ryan N, Kennard B, Hughes C, DeBar L, McCracken J, Strober M, Suddath R, Spirito A, Leonard H, Melhem N, Porta G, Onorato M, Zelazny J. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized controlled trial. JAMA. 2008;299(8):901-913.

- Blader JC, Schooler NR, Jensen PS, Pliszka SR, Kafantaris V. Adjunctive divalproex sodium vs. placebo for children with ADHD and aggression refractory to stimulant monotherapy. Am J Psychiatry. 2009;166(12):1392-1401

GENERAL DISCUSSION
Benedetto Vitiello, M.D.
NIMH

WORKSHOP
3:00 PM – 6:00 PM
WORKSHOP OVERVIEW:
THE UNDER UTILIZATION OF CLOZAPINE: REASONS AND SOLUTIONS
J.P. Lindenmayer, M.D.[1], Herbert Y. Meltzer, M.D.[2], Peter Buckley, M.D.[3], Ira Glick, M.D.[4]
[1]New York University School of Medicine, [2]Northwestern University, Feinberg School of Medicine, [3]Georgia Health Sciences University, [4]Department of Psychiatry & Behavioral Sciences Stanford University School of Medicine
Clozapine remains the most effective antipsychotic available today. In spite of demonstrable efficacy and superiority to other agents and near unanimous recommendations that clozapine should be used early on in any patient not fully recovered from psychosis, it is not. Patients receiving clozapine typically receive it years after they are qualified to, and many more never receive a trial at all. Clozapine's underutilization remains the quintessential "science to service gap" in behavioral medicine.This panel will present data underlying the specific indications for clozapine in support of wider utilization, factors contributing to the under-utilization and innovative solutions to increase it. This first presentation will present the data underlying the two specific indications for clozapine in support of wider utilization. A second presentation will focus on the key factors for this underutilization, such as the burden of hematological testing and concern over adverse events; poor recognition of treatment refractory states, including its suicide protection indication and the easy access to polypharmacy. A third presentation will present a comprehensive approach implemented in a large public mental health delivery system aimed at increasing clozapine utilization both in the inpatient and outpatient areas. A fourth presentation will focus on other innovative proposals for its greater usage, such as creating specialty clinics, increasing reimbursement rates and bed-side blood testing devices.
Learning Objectives:
- After the presentation participants will be aware of clozapine's specific indications and superiority compared to other antipsychotics in patients with schizophrenia
- During this presenation participants will learn about methods, interventions and policy proposals to increase the utilization of clozapine.

INDIVIDUAL ABSTRACT:
LACK OF KNOWLEDGE OF THE BENEFITS OF CLOZAPINE FOR PERSISTENT PSYCHOSIS AND SUICIDE RISK ALONG WITH OVERESTIMATION OF THE DANGERS OF AGRANULOCYTOSIS LIMIT ITS UTILIZATION
Herbert Y. Meltzer, M.D.
Northwestern University, Feinberg School of Medicine
Clozapine has important quantitative and qualitative advantages over all typical and some atypical antipsychotic drugs: efficacy in treatment resistant schizophrenia, ability to reduce the risk for suicide, and improvement in some domains of cognition, e.g.semantic and declarative

memory. Only the latter is disputed, perhaps because of lack of consideration of the evidence from meta-analyses which take into account practice effects and the magnitude of improvement in these domains, which far exceeds the practice effect, especially for semantic memory. Clozapine is often referred to as the 'gold standard' for treatment of schizophrenia. It has been suggested to be considered a first line treatment, despite its many side effects, because of its overall effect on mortality in schizophrenia, based mainly on its profound antisuicidal effect (Tiihonen et al. 2009). Yet, it is underutilized in the US for treatment resistant patients and those who are at high risk for suicide, despite the fact that it is the only antipsychotic drug with FDA approval for these indication (Horvitz Lennon et al. 2009). Limited knowledge of benefits and risks as well as how to utilize the drug in mental health centers is the major cause of underutilization. Agranulocytosis and myocarditis, the two most serious side effectscan be managed as can virtually all of its side effects. With appropriate clinic management techniques, the burden on clinicians can be managed. Education of patients and caregivers can lead to high acceptance rates, as has been demonstrated in a number of European countries.

Learning Objectives:
- To become familiar with the evidence in support of the antidepressant properties of NK1 antagonists
- How Nk1 antagonists can deliver a differentiated antidepressant profile

Literature References:
- Meltzer HY. Clozapine.Clin Schizophr Relat Psychoses. 2012 Oct;6(3):134-44
- Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. 2009 Aug 22;374(9690):620-7.
- Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol. 2010 Jul;24(7):965-71.
- Horvitz-Lennon M, Donohue JM, Domino ME, Normand SL. Improving quality and diffusing best practices: the case of schizophrenia. Health Aff (Millwood). 2009;28(3):701-12.

INDIVIDUAL ABSTRACT:
EFFICACY OF CLOZAPINE AND REASONS UNDER UTILIZATION
Ira Glick, M.D.
Department of Psychiatry & Behavioral Sciences Stanford University School of Medicine
This presentation will review the efficacy of clozapine compared to other first and second-generation antipsychotics. We have done (2011) a meta-analysis of controlled and naturalistic studies for both short and long-term efficacy. Results suggested clozapine is the most effective of all antipsychotics. Given that this data has been available for many years, reasons for underutilization will be discussed.

Learning Objectives:
- Efficacy data comparing clozapine to other antipsychotics
- Reasons why clozapine is underutilized in practice

Literature References:
- Glick I, Corral C. Altamura c et al, Mid and Long-term Efficacy of Antipsychotics for the Treatment of Schizophrenia, J Clin Psychiatry, dec, 2011
- Nielson J. et al, Predictors of Clozapine Response in Patients with Treatment-refractory Schizophrenia, J Clinical Psychiatry 12: 678-683, 2012

INDIVIDUAL ABSTRACT:
A MULTI-DIMENSIONAL CLOZAPINE UTILIZATION CAMPAIGN IN A PUBLIC PSYCHIATRIC SETTING

J.P. Lindenmayer, M.D.
New York University School of Medicine

A consensus developed in the New York State Office of Mental Health (OMH) that clozapine was underutilized in all OMH operated services (14% of patients served were on clozapine in 2011) and throughout New York State (6% of Medicaid recipients receiving antipsychotic medications were on clozapine). Under the leadership of its chief medical officer and its Commissioner, the Office of Mental Health set out to increase the appropriate and safe utilization of clozapine by initiating a campaign grounded in clinical knowledge, peer and family leadership. The campaign steering group developed clear, defined, measurable goals, identified supporting and resisting forces, identified support of key stakeholders and those who may bring resources to this effort, identified proven and feasible, and affordable interventions. Target population were adults in OMH operated outpatient and inpatient services. Training materials were developed for consumers and families, for doctors, nurses and other clinical staff including videos, webinars, learning collaboratives and informational brochures and medical informational documents. Each inpatient service and outpatient clinic appointed a campaign 'captain' who joined in regular monthly telephone conferences. Immediate, phone consultations by clozapine experts were made available. Regular feed back of clozapine utilization rates was provided to all clinicians and administrators with target numbers set by the steering committee. Results in change in clozapine utilization rates and contributing factors will be presented.

Learning Objectives:
- After this presenation participants will understand the different interventions used in a large public psychiatric system desigend to increase the utilization of clozapine
- Participants will learn the results of this multi-dimensional intervention and factor s contributing to the increase in utilization of clozapine.

Literature References:
- Volavka J. Czobor P. Sheitman B. Lindenmayer JP. Citrome L. McEvoy JP. Cooper TB. Chakos M. Lieberman JA.Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder.[see comment][erratum appears in Am J Psychiatry 2002 Dec;159(12):2132].
- Lindenmayer JP, Kanellopoulou I. Schizophrenia with impulsive and aggressive behaviors.Psychiatr Clin North Am. 2009;32(4):885-902.

INDIVIDUAL ABSTRACT:
THE UNDER UTILIZATION OF CLOZAPINE: REASONS AND SOLUTIONS

Peter Buckley, M.D.
Georgia Health Sciences University

Our field has struggled about when to introduce clozapine- unequivocally the more powerful antipsychotic medication for this recalcitrant population- and at present this 'drug of choice' for treatment-refractory schizophrenia is introduced too late in the course of the illness more often than not. The reason for this is the (variable) effacy of other available antipsychotics in this population, although the sequential availability of each new antipsychotic seems to relegate clozapine's use even- further away from early illness. Once clozapine is tried, a portion of

patients will inevitably have an unsatisfactory outcome and how nest to next treat these patients remains another clinical conundrum. This presentation will outline innovative approaches to enhance clozapine use including resident experiences, algorithm-driven choices, extending specialty clinics, evaluating reimbursement rates, and the coming on-line of bed-side testing devices.

Learning Objectives:
- Discuss innovative approaches increase the utilization of clozapine.
- Discuss current concerns of trainees getting inadequate experience with clozapine and the implications this has on its under-utilization.

Literature References:
- Nielsen J et al. Geographical and temporal variations in clozapine prescription for schizophrenia. European Neuropsychopharmacology (2012) 22:11; 818–824
- Nielsen J et al. 10-Year trends in the treatment and outcomes of patients with first-episode schizophrenia. Acta Psychiatr Scand 2010: 122: 356–366.

GENERAL DISCUSSION

J.P. Lindenmayer, M.D.
New York University School of Medicine

Thursday, May 30, 2013

PLENARY SESSION
8:30 AM – 10:00 AM
PLENARY SESSION OVERVIEW:
NEW FDA & EMA INITIATIVES IN ALZHEIMER'S DISEASE, DEPRESSION AND SCHIZOPHRENIA

Karl Broich, M.D.
Federal Institute for Drugs and Medical Devices, BfArM, Germany

This session will provide an update from FDA and EMA in several different topic areas of current interest. Karl Broich from BfArM will discuss recent developments on EMA's approach to biomarker qualification, using Alzheimer's disease as an example. Ni Khin from FDA will present preliminary exploratory findings from a recently established patient-level database involving approximately 7800 patients with MDD. Exploratory findings will include the effect of trial duration, the effects of various definitions of sustained response, and optimization of rating scale item subgroupings, all with regard to the efficiency of drug/placebo discrimination. Islam Younis from FDA will present preliminary exploratory findings from a recently established patient-level database involving patients with schizophrenia. His analyses will also explore trial duration, different study endpoints, and other design features, with the goal of discovering approaches to increase the efficiency of schizophrenia drug development programs.

INDIVIDUAL ABSTRACT:
BIOMARKERS IN DRUG DEVELOPMENT BETWEEN HYPE AND HOPE: THE QUALIFICATION PROCESS AT EMA

Karl Broich, M.D.
Federal Institute for Drugs and Medical Devices, BfArM, Germany

Biomarkers have become a popular topic in many fields of medicine and all stages of drug development. Recent progress in basic research coupled with advances in various types of 'omics and neuroimaging in large data bases has fostered hope that drug development, diagnostic procedures and clinical management of CNS disorders will be challenged. From a regulatory point of view biomarkers can already be used to better define homogeneous study populations and to select the most promising drug candidates in their effective dosages for phase III clinical trials, however, further qualification and validation of specific biomarkers in large-scale international controlled multicenter studies is necessary before they can be accepted as primary outcome measures in pivotal phase III clinical trials - until now no biomarker has been sufficiently validated to be acceptable as a surrogate endpoint in pivotal CNS clinical trials. Establishing biomarkers as surrogate endpoints is an important goal particularly in conditions like Alzheimer's disease, especially in their early (preclinical, presymptomatic) stages, as traditional clinical outcome measures might be too insensitive to change or need unfeasible treatment durations for clinical trial conditions. Improvements can only be accomplished by active synergistic collaboration between academic, industrial and regulatory partners. Therefore EMA updated the guidance document to applicants on 'Qualification of novel methodologies for drug development'. The EMA approach and experience from qualification procedures for biomarkers in Alzheimer's disease will be provided.

INDIVIDUAL ABSTRACT:

UPDATE ON FDA EXPLORATORY ANALYSES OF AGGREGATED EFFICACY DATA FROM DEPRESSION TRIALS
Ni Khin, M.D.
Food and Drug Administration
Reports of rising placebo response, declining treatment effects, and substantial failure rates in depression trials are of great concern. There have been exploratory analyses of trial-level data to investigate these trends, however, these approaches have significant limitations with regard to identifying possible contributing factors. To address this problem, we recently established a pilot patient-level database, comprised of approximately 7800 patients with major depressive disorder who were enrolled in short-term randomized controlled trials. Exploratory analyses of this dataset have been initiated to evaluate the effect of trial duration and different endpoints, including various definitions of sustained treatment response and various rating scale item subsets, on trial efficiency. Preliminary findings from these analyses will be presented.

INDIVIDUAL ABSTRACT:
FDA INITIATIVE TO OPTIMIZE DESIGN ELEMENTS OF SCHIZOPHRENIA DRUG TRIALS
Islam Younis, Bs.C., Ms.C., Ph.D.
Reports of rising placebo response, declining treatment effects, and substantial failure rates in schizophrenia trials are of great concern. There have been exploratory analyses of trial-level data to investigate these trends, however, these approaches have significant limitations with regard to identifying possible contributing factors. To address this problem, we recently established a pilot patient-level database from short-term randomized controlled trials in patients with schizophrenia. Exploratory analyses of this dataset have been initiated to evaluate the effect of trial duration and different endpoints, including various rating scale item subsets, on trial efficiency. The goal is to optimize trial design and increase the efficiency of schizophrenia drug development programs. Details of the initiative and preliminary findings will be discussed.
GENERAL DISCUSSION
Karl Broich, M.D.
Federal Institute for Drugs and Medical Devices, BfArM, Germany

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PANEL
10:15 AM – 11:45 AM
PANEL OVERVIEW:
CLOZAPINE: HOW FAR HAVE WE COME?
John M. Kane, M.D.[1], Donald Goff, M.D.[2], Thomas Laughren, M.D., Christoph U. Correll, M.D.[4]
[1]The Zucker Hillside Hospital, [2]New York University Medical Center, [4]Hofstra North Shore-LIJ School of Medicine
Despite the emphasis placed on the implementation of evidence based practices in contemporary health care, there remains an enormous gap and delay in the translation of research findings into routine clinical practice. This panel will focus on current knowledge and practice regarding clozapine, which remains the only evidence-based alternative for those patients who fail to respond adequately to other antipsychotic medications. The aim is to review the latest evidence from controlled and population based studies for the efficacy, effectiveness and safety of clozapine, to identify barriers to the appropriate use of clozapine, and to point to potential

solutions to increase the utilization of clozapine in patients refractory to other treatment options without inappropriate delay or trials of less well proven treatment options.

Across multiple guidelines, clozapine is recommended as a second-line treatment after failure of at least two adequate antipsychotic trials. Despite current estimates that 25%-40% of schizophrenia patients would be candidates for clozapine treatment, only less than 10% of schizophrenia patients are treated with clozapine. Barriers to clozapine utilization include insufficient knowledge of indications and appropriate timing of clozapine implementation, inexperience with its use, fear of adverse effects, particularly agranulocystosis, lack of administrative and clinical support for managing potential problems associated with clozapine use, insufficient appreciation of potential impact on functional outcome and subjective well-being.

Learning Objectives:
- To be familiar with current evidence and guidelines regarding clozapine use
- To understand factors which influence physician attitudes and utilization

INDIVIDUAL ABSTRACT:
AN UPDATE ON THE QUEST TO IDENTIFY CLOZAPINE'S MECHANISMS OF ACTION
Donald Goff, M.D.
New York University Medical Center

Fifty years after clozapine was first synthesized and 20 years after introduction to the US market, the mechanism(s) of action responsible for clozapine's superior efficacy remain a mystery. Given the relatively low rate at which clozapine is prescribed and the serious, potentially life-shortening metabolic consequences, the development of agents that share clozapine's efficacy without its limiting side effects is of critical importance for treatment refractory patients with schizophrenia. This talk will provide an update by reviewing and synthesizing new evidence from studies examining clozapine's mechanism of action.

Many models have been proposed to explain clozapine's unique clinical profile, including a high ratio of 5HT2/D2 occupancy, a high dissociation constant for D2 binding and activity at adrenergic and muscarinic receptors. In addition, considerable evidence points towards clozapine's unique activity on glutamatergic systems, possibly in combination with activation of prefrontal cortical D1 receptors. More recently, attention has focused on the possible role of insulin signaling pathways, neuroactive steroid induction, mitogen-activated protein kinase (MAPK) signal transduction pathways, DNA demethylation effects, and neuroprotective effects possibly mediated via neurotrophins.

Recent evidence from microbiology, animal models, human studies, and postmortem analyses will be reviewed, with an emphasis upon the predictive power of each model to differentiate first from second generation agents and clozapine from all other antipsychotics. The clinical performance of therapeutic agents developed on the basis of each of the proposed biochemical strategies, when available, will also be reviewed.

Learning Objectives:
- Participants will understand the effect of antipsychotic treatment on adiposity.
- Participants will understand the effect of antipsychotic treatment on insulin sensitivity.

Literature References:
- Yang CR, Chen L. Targeting prefrontal cortical dopamine D1 and N-methyl-D-aspartate receptor interactions in schizophrenia treatment. Neuroscientist 2005; 11:452-470.

- Guidotti A, et al. Epigenetic GABAergic targets in schizophrenia and bipolar disorder. Neuropharmacology 2011; 60:1007-1016.

INDIVIDUAL ABSTRACT:
CLOZAPINE: EVIDENCE, GUIDELINES AND OBSTACLES TO UTILIZATION
John M. Kane, M.D.
The Zucker Hillside Hospital

Background: Almost 25 years after its approval by the FDA, clozapine remains the only evidenced based treatment for those patients who fail to respond adequately to other antipsychotic agents. In addition, clozapine is the only antipsychotic drug with an indication for the prevention of suicidality in schizophrenia. Despite the prevalence of these indications in clinical practice, clozapine utilization varies widely from country to country and remains remarkably low in the U.S.

Methods: Review of all meta-analyses that have been conducted over the past five years. Review of current guidelines (e.g. APA, PORT, NICE, TMAP, CPA, etc.) regarding the use of clozapine. Review of available utilization rates from a variety of countries in North and South America, Europe, Asia and Australia/New Zealand. Review of studies that have been conducted in various countries regarding physician attitudes toward clozapine use and perceived obstacles, as well as patients' perceived obstacles. Ongoing survey of 1,000 plus physicians in the U.S., Canada, Brazil, Denmark, Taiwan, China, Greece, Korea and Portugal regarding knowledge, attitudes, perceived obstacles and utilization rates of clozapine.

Results: With some exceptions (e.g. Leucht 2009), meta-analyses are consistent in showing superiority for clozapine. Potential reasons for discrepancies include patient selection and dosing. The published guidelines for clozapine use are consistent in suggesting that it should be considered after the failure of two adequate trials of other antipsychotics (the use of an FGA as one of those two drugs is a variable in the recommendations). The recommendations are less specific as to what duration constitutes an adequate trial. Utilization rates across nine countries vary from less than 5% to more than 30%. Such differences suggest variability in physician practice/health care policy rather than the epidemiology of treatment resistance. Surveys of physician attitudes suggest that concerns regarding weight gain and metabolic adverse effects, blood monitoring and the risk of agranulocytosis remain foremost in physicians' minds.

Conclusions: As is too often the case in healthcare, the application of evidenced based practice in routine clinical care falls far short of expectations. Our ability to understand and impact this disconnect will depend on a thorough understanding of the true nature of the obstacles and what strategies are likely to be most successful in overcoming them in particular clinical , economic and cultural environments.

Learning Objectives:
- To be familiar with current evidence and guidelines regarding clozapine use.
- To understand factors which influence physician attitudes and utilization.

Literature References:
- Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev. 2009 Jan 21;(1): CD000059
- Nielsen J, Dahm, Lublin H, Taylor D. Psychiatrist's attitude towards and knowledge of clozapine treatment. J Psychopharmacol. 2010 Jul;24(7):965-71
- Leucht S. Komossa K. Rummel-Kluge C. Corves C. Hunger H. Schmid F. Asenjo Lobos C. Schwarz S. Davis JM. A meta-analysis of head-to-head comparisons of second-

generation antipsychotics in the treatment of schizophrenia. American Journal of Psychiatry. 166(2):152-63, 2009

INDIVIDUAL ABSTRACT:
INCREASING UTILIZATION OF CLOZAPINE THROUGH KNOWLEDGE ABOUT RISK FACTORS FOR AND MANAGEMENT OF SERIOUS AND NON-SERIOUS ADVERSE EFFECTS

Christoph U. Correll, M.D.
Hofstra North Shore-LIJ School of Medicine

Background: Despite being the only alternative treatment for many patients with inadequately responding schizophrenia, clozapine remains highly underutilized. One reason for this is the potential for severe adverse effects that clinicians are insufficiently trained to manage.
Methods: Summary of the frequency, risk factors and management for both severe/potentially life-threatening adverse effects requiring discontinuation, as well as manageable adverse effects that should not lead to discontinuation. Covered side effects include sedation/somnolence, constipation, sialorrhea, myocarditis, tachycardia, drug-induced fever, weight gain, metabolic abnormalities and blood dyscrasias. In addition, emerging biomarkers are discussed.
Results: In an unpublished meta-analysis of 35 randomized controlled trials in strictly defined refractory schizophrenia, 24 trials, lasting 13.7 ± 10.7 weeks (n= 2,537), included clozapine. Compared to atypical (13 trials) or typical (11 trials) antipsychotics, clozapine had significantly greater sedation (RR:2.07 (95%CI:1.17-3.64), p=0.01) and increases in triglycerides (Hedge's g:0.26 (95%CI:0.05-0.46), p=0.01) and glucose (Hedges g:0.54 (95%CI:0.15-0.92), p=0.006). Recently, the association of severe weight gain with a SNP in the melanocortin-4 receptor in a discovery sample of 139 antipsychotic-naïve youth was confirmed in a clozapine treated sample, naïve to atypical antipsychotics. Other pharmacogenomic predictors of weight gain will be presented from an ongoing meta-analysis with 30 studies focusing on clozapine. Furthermore, in a preliminary whole-genome association study, a single SNP (6672G>C) in HLA-DQB1 was found in 2 cohorts that was associated with a 16.9 times greater risk for clozapine associated agranulocytosis. Eosinophilia alone, however, was an unreliable predictor of agranulocytosis. Clozapine induced side effects that should and should not lead to clozapine discontinuation will be summarized and management strategies, including re-challenge options, will be presented.
Discussion: Clozapine's greater association with certain adverse effects compared to other antipsychotics interferes with its more widespread use in treatment refractory schizophrenia patients. Identifying and utilizing biomarkers of specific adverse effects can help personalize treatment and identify novel drug development targets for side effect amelioration. Improved familiarity of clinicians with adverse effects and management strategies is needed.
Learning Objectives:
- Increase knowledge and competence in dealing with adverse effects of clozapine
- Incorporate knowledge about management strategies into clinical care

Literature References:
- Nielsen J, Correll CU, Manu P, Kane JM. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? – under review
- Manu P, Sarpal D, Muir O, Kane JM, Correll CU. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. Schizophr Res. 2012 Feb;134(2-3):180-6.

- Kishi T, Kishimoto T, Nielsen J, Zhang JP, Kane JM, Correll CU. Efficacy and tolerability of antipsychotics in treatment-resistant schizophrenia: Systematic review and meta-analysis. – unpublished.

GENERAL DISCUSSION
Thomas Laughren, M.D.

PANEL
10:15 AM – 11:45 AM
PANEL OVERVIEW:
FORMAL ASSESSMENT OF SUICIDAL IDEATION, BEHAVIOR AND RISK IN CLINICAL TRIALS AND EMERGENCY SETTINGS: IMPLICATIONS OF RECENT RESEARCH

Alan J. Gelenberg, M.D.[1], Michael E. Thase, M.D.[2], Maria Oquendo, M.D.[3], Phillip Chappell, M.D.[4], Cheryl McCullumsmith, M.D., Ph.D.[5], Ahmad Hameed, M.D.[6]
[1]Penn State University, [2]Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center, [3]Columbia University and New York State Psychiatric Institute, [4]Pfizer, Inc, [5]University of Alabama at Birmingham, Department of Psychiatry and Behavioral Neurobiology, [6]Penn State Milton S. Hershey Medical Center and College of Medicine

There has been a tremendous increase in interest in the formal assessment of suicidal ideation behavior and risk: 1) in relationship to FDA concerns about treatment emergent effects of CNS drugs; 2) in the context of the need to develop efficacious treatments to reduce risk of suicide in high risk patients; and, 3) in the context of clinical assessments in emergency settings (with associated concerns about predictive validity and the collection of valid epidemiological data on suicide across the age span). It is now 5 years since the FDA advisory documents were published related to concerns about treatment emergent suicidal ideation and behavior in relationship to antidepressant drug treatments in children and adolescents, and in patients being treated with anti-seizure medication. What have the results been as industry has introduced formal assessment for treatment emergent suicidal ideation and/or behavior? Have any of the most often used assessment instruments clearly identified treatment emergent concerns over this time period? What have been the operational aspects involved in the implementation of different formal assessments? With the introduction of new assessment tools, what have been the ramifications in emergency settings re: the clinical assessment of suicide risk?

Finally, studies in patients with schizophrenia and patients with bipolar disorder have demonstrated the feasibility and utility of assessing the impact of different approved treatments on suicidal ideation; and pilot data suggests the potential efficacy of an NMDA receptor antagonist in reducing suicidal ideation in treatment resistant depressed patients. Are the FDA endorsed criteria on assessment of suicidal ideation and behavior sufficient and validated in the context of trials assessing them as primary outcomes?

Learning Objectives:
- Appreciate methodologic challenges in assessing suicidality in clinical populations
- Understand current state of assessing and managing patients in emergency settings and clinical research

INDIVIDUAL ABSTRACT:

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

Ahmad Hameed, M.D.
Penn State Milton S. Hershey Medical Center and College of Medicine

Clinical and Operational Aspects of the Columbia Suicide Severity Rating Scale (C-SSRS) and Sheehan Suicide Tracking Scale (STS and S-STS) in a Psychometric Evaluation Study

Background: There has been a tremendous increase in interest in the formal assessment of suicidal ideation behavior. In the context of FDA guidance and recommendations, a new generation of assessment instruments has emerged to document treatment emergent "suicidality" in all clinical CNS drug trials. In its most recent draft Guidance Document, the Agency made additional specific recommendations. At the same time, apart from studies performed by the developers of these instruments, little is known about the comparative operational aspects, psychometric properties, patient and investigator perceptions of using the instruments, or the differences and similarities of data obtained with the different approaches. Moreover, because actual suicide is a relatively rare event, none of the new generation of assessment instruments has been evaluated for predictive validity.

Study: Between January and November 2012, we conducted a psychometric evaluation study comparing three different approaches to the assessment of suicidal ideation and behavior in 200 psychiatric inpatients. Participants included subjects with the full range of diagnoses associated with acute psychiatric admissions. The study compared data obtained with the clinician-administered version of the Columbia Suicide Severity Rating Scale (C-SSRS), with clinician and self-report versions of the Sheehan Suicidality Track Scale (S-STS). In a participant sample likely to include a substantial percentage of patients with suicidal ideation and/or recent behavior, we specifically assessed the psychometric properties of each instrument, patient and rater satisfaction, and operational aspects (including training requirements, inter-rater reliability and actual time to administer each scale). In addition, the researchers extracted clinical data from patient records, including possible re-admission within 30 days of discharge from the index admission.

Outcome/Results:
* Average time taken complete each
* Patient satisfaction
* Correlation between clinical presentation and S-STS and C-SSRS?
* Predictive value

Discussion: This is the first formal comparison of the C-SSRS and the Sheehan Suicide Tracking Scale. In addition to comparing operational aspects of the scales, we will present information on the clinical challenges that came up consistently during the study that need to be considered in future training and quality improvement efforts. (e.g., clinical interviews and necessary inter-personal skills, past month vs lifetime, aborted attempt vs preparatory behavior). The results have significant implications for industry sponsored CNS clinical drug trials and other applications related to these assessment instruments, as well as for regulatory agencies.

Reference:
1. Meyer et al. (2010). Suicidality and risk of suicide- definition, drug safety concerns, and a necessary target for drug development: a consensus statement. Journal of Clinical Psychiatry, 71(8), e1-e21.

2. Posner et al. (2011). The Columbia- Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry. 168(12), 1266-1277.
3. Coric, V., Stock, E.G., Pultz, J., Marcus, R., & Sheehan, D.V. (2009). Sheehan Suicidality Tracking Scale (Sheehan-STS): Preliminary results from a multicenter clinical trial in generalized anxiety disorder. Psychiatry (Edgmont), 6(1), 26-31.
4. Shea, S.C. (2009). Suicide Assessment: Part 1 - Uncovering Suicidal Intent: ASophisticated Art. Psychiatric Times. 26 (12).
5. Suppiger A, In-Albon T, Hendriksen S, Hermann E, Margraf J, Schneider S. Acceptance of structured diagnostic interviews for mental disorders in clinical practice and research settings. Behav Ther. 2009; 40:272-9.

Learning Objectives:
- To unravel the psychobiological mechanisms undelying placebo effects.
- To understand the potential interaction between placebo and drug effects.

Literature References:
- Meyer et al. (2010). Suicidality and risk of suicide- definition, drug safety concerns, and a necessary target for drug development: a consensus statement. Journal of Clinical Psychiatry, 71(8), e1-e21.
- Posner et al. (2011). The Columbia- Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry. 168(12), 1266-1277.

INDIVIDUAL ABSTRACT:
PROSPECTIVE ASSESSMENT OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL TRIALS: A PHARMA PERSPECTIVE
Phillip Chappell, M.D.
Pfizer, Inc.

This presentation will review the response of pharma to FDA's original draft guidance to industry on the prospective assessment of suicidal ideation and behavior (SIB) in clinical trials (September 2010), with a focus on the development and implementation of the Pfizer internal guidance for its drug development teams on how to determine whether prospective SIB assessments are required, how the assessments should be implemented, and how the data should be analyzed. A review of the Pfizer experience to date will be presented including the type of clinical studies which have implemented prospective assessments, their indications, phase of development, and the choice of SIB assessment instrument used. Continuing operational challenges encountered in the implementation of prospective SIB assessments will be discussed (including issues such as version control, availability of translations, the need for cultural validation, quality of rater training and experience, and the need for study sites to identify mental health experts for referral of patients identified as being at risk of suicide), as well as the implications and challenges of the recent revision of the draft FDA guidance in August 2012. There remain significant challenges of assessment of SIB in special populations, such as patients with dementia, autism, or acute neurologic or medical conditions (ie, stroke and other life-threatening conditions) and in prepubertal children. An urgent need exists to examine the performance of the available SIB assessment instruments in special populations, such as children and patients with dementia. Studies of patients with mild cognitive impairment or Alzheimer's Disease increasingly include prospective SIB assessments in the absence of any established

objective guidelines on the use of these assessments in patients at different stages of cognitive decline. As in the case of young children, no separate validity and reliability data are available on the use of any SIB assessment in cognitively impaired patients, despite the widespread implementation of SIB assessments in industry sponsored trials in dementia patients. The challenge of assessing young children (e.g., < 11 years down to 5-6 years of age) who may not have reached sufficient cognitive maturity to understand the concept of death is acknowledged in the revised FDA Guidelines (August 2012), but empirical evidence of the psychometric properties of existing scales, their linguistic validation from a developmental perspective, and ages at which children can understand these concepts is urgently needed.

Extensive datasets of prospective SIB assessments from clinical trials conducted in many different patient populations across many different geographic regions are rapidly accumulating and ultimately will be analyzed for signal detection of suicidal ideation and behavior. The results of these analyses will be valid and reliable only to the extent that the SIB assessment tools employed are demonstrated to be valid and reliable in the diverse patient populations, geographic locations and cultures to which their use has been rapidly extended.

Learning Objectives:
- Awareness of the challenges of conducting valid SIB assessments in special populations such as patients with dementia, autism, acute life-threatening conditions, and pre-pubertal children and implications for the validity of the data obtained using current assessment methods in these patient populations.
- Awareness of the challenges of conducting valid SIB assessments in special populations such as patients with dementia, autism, acute life-threatening conditions, and pre-pubertal children and implications for the validity of the data obtained using current assessment methods in these patient populations.

Literature References:
- Guidance for Industry, Suicidality: Prospective Assessment of Occurrence in Clinical Trials, September 2010). U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)
- Guidance for Industry, Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, August 2012) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)
- Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ: The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011; 168:1266–1277
- Chappell PB, Feltner DE, Makumi C, Stewart M. Initial validity and reliability data on the Columbia-Suicide Severity Scale. [Letter to the Editor]. Amer J of Psychiatry 169:6, June 2012.

INDIVIDUAL ABSTRACT:
IV KETAMINE FOR TREATMENT OF ACUTE SUICIDAL IDEATION FOR PATIENTS WITH DEPRESSION IN THE EMERGENCY DEPARTMENT
Cheryl Mccullumsmith, M.D., Ph.D.
University of Alabama at Birmingham, Department of Psychiatry and Behavioral Neurobiology

Background: There are approximately 580,000 ED visits associated with a primary diagnosis of depression each year and more than half result in admission. The suicide mortality rate for is these patients is very high. In spite of this compelling need, there are now no rapidly effective treatments for depression and suicidal ideation employed in the ED.The competitive NMDA antagonist ketamine has shown promise as a rapidly acting treatment for both depression and suicide. In spite of these very promising results, there has only been one small published study of ketamine in the most logical setting for acute administration, the ED.

Study Design: *Participants:* Patients presenting to the UAB ED with a major depressive disorder and acute suicidal ideation. *Exclusions:* Patients were excluded from study entry if they were medically unstable, using illicit drugs, pregnant or lactating or had psychosis or mania. *Treatment:* A single IV dose of 0.2 mg/kg IV ketamine or saline. *Assessments:* Montgomery Asberg Depression Rating Scale (MADRS)and the Beck Scale for Suicidal Ideation for 4 hours and days 1-7, 10, and 14. *Analysis:* ANOVA and logistic regression using SPSS.

Results: Patients who received ketamine had a rapid decrease in suicidality as measured by both the Beck Scale for Suicidal Ideation and the MADRS suicide, within the first 15 minutes after infusion, and persisted for over the full 14 days of follow-up. The suicidality of placebo-treated participants gradually declined over the 2 weeks, reflecting ongoing treatment. Dpression, as measured by MADRS scores, dropped in both groups with the ketamine group showing more rapid change over the first four hours. There were no serious adverse events in either group.

Discussion: These preliminary data indicate that ketamine infusion in is feasible, safe, and may be effective for the treatment of suicidal depression in the ED. If confirmed, these findings could represent a paradigm shift in the treatment of acutely depressed and suicidal ED patients. Further studies examining these outcomes and long term studies as well as studies in acute suicidality associated with other mental illnesses remain to be tested. This presentation will also discuss the predictive value and limitations of standard assessment scales when used in the ED setting.

Learning Objectives:
- To understand the preliminary evidence for usefulness of ketamine as an acute treatment for suicidality in the emergency department setting
- To understand the benefits and limitations of currently available suicidality measures in measuring acute changes in suicidality

Literature References:
- Mathew Sj, Shah A, Lapidus K, Et Al. Ketamine For Treatment-Resistant Unipolar Depression: Current Evidence. Cns Drugs. Mar 2012;26(3):189-204
- Larkin Gl, Beautrais Al. A Preliminary Naturalistic Study Of Low-Dose Ketamine For Depression And Suicide Ideation In The Emergency Department. Int J Neuropsychopharmacol. Sep 2011;14(8):1127-1131.

INDIVIDUAL ABSTRACT:
ASSESSING EFFICACY WHEN THE OUTCOME MEASURES ARE SUICIDAL IDEATION OR BEHAVIOR: FOCUS ON HIGH RISK POPULATIONS
Maria Oquendo, M.D.
Columbia University and New York State Psychiatric Institute
Trials focused on suicidal ideation and suicidal behavior present special design challenges. As a field, we have limited experience with such studies. Yet, with suicide now exceeding the death

rate due to motor vehicle accidents, suicidal behavior and its antecedents require our urgent attention.

Studies of suicidal ideation are tricky for at least two reasons: 1) because of its inherent volatility; and 2) because we are interested in decreasing it as quickly as possible. Consequently, RCTs must employ analyses that examine the time-varying effects of specific treatments on suicidal ideation. State of the art statistical methods, such as mixed effects models, that use "all the data" from longitudinal repeated measures may be important. Also drug effects may well be more salient in those with greater suicidal ideation, making analytic strategies to assess moderating variables (e.g. baseline severity) essential. Similarly, identification of mediators of change would go a long way to providing possible treatment targets to decrease risk. For example, were abatement of psychic anxiety found to mediate decreases in suicidal ideation, this would advance the search for anti-suicidal interventions.

Even thornier are design issues for RCTs focused on suicide attempts. First, because these are low base rate outcomes, selecting high risk populations for study becomes essential. Critically, the investigator must actively try to prevent the outcome of interest, suicide attempt or suicide, creating a major challenge to statistical power and its accurate estimation. Surrogate measures such as "suicide event" can be used to circumvent this problem, but they create other hazards. A suicide event is operationalized as an increase in suicidal ideation and planning to a predetermined threshold that requires the investigator to make a change in the treatment (hospitalization, increase in frequency of visits, or others) to "prevent" an attempt. However, use of such proxy outcomes, while having clinical "face validity," necessarily reduces the interpretability of results, since the investigator cannot be certain that a suicide or suicide attempt would have occurred had s/he not intervened.

Challenges in assessing efficacy of interventions for suicidal ideation and behavior are related to both ethical and clinical considerations. They require creative study design for optimal interpretability and utility.

Learning Objectives:
- Participants will be able to identify suicide related outcome measures appropriate for use in high risk populations
- Participants will be familiar with design strategies useful when the outcome variable may be influenced by the investigator's intervention

Literature References:
- Grunebaum MF, Ellis SP, Duan N, Burke AK, Oquendo MA, John Mann J. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. Neuropsychopharmacology. 2012 Feb;37(3):697-706.
- Oquendo MA, Galfalvy HC, Currier D, Grunebaum MF, Sher L, Sullivan GM, Burke AK, Harkavy-Friedman J, Sublette ME, Parsey RV, Mann JJ. Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. Am J Psychiatry. 2011;168(10):1050-6.
- Brent DA, Greenhill LL, Compton S, Emslie G, Wells K, Walkup JT, Vitiello B, Bukstein O, Stanley B, Posner K, Kennard BD, Cwik MF, Wagner A, Coffey B, March JS, Riddle M, Goldstein T, Curry J, Barnett S, Capasso L, Zelazny J, Hughes J, Shen S, Gugga SS, Turner JB. The Treatment of Adolescent Suicide Attempters study (TASA): predictors of suicidal events in an open treatment trial. J Am Acad Child Adolesc Psychiatry. 2009 Oct;48(10):987-96.

GENERAL DISCUSSION

Michael E. Thase, M.D.
Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center

PANEL
10:15 AM – 11:45 AM
PANEL OVERVIEW:
NIAAA SPONSORED PANEL: WHEN ONE DRINK IS NOT ENOUGH: RECENT CONSIDERATIONS OF DRINKING OUTCOME MEASURES FOR ALCOHOL CLININAL TRAILS FROM THE ACTIVE WORKGROUP

Raymond F. Anton, M.D.[1], Celia Winchell, M.D.[2], Michael Buehlen, M.D.[3], Raye Z. Litten, III, Ph.D.[4]
[1]Dept. of Psychiatry, Medical University of South Carolina, [2]Center for Drug Evaluation and Research, Food and Drug Administration, [3]Federal Institute for Drugs and Medical Devices (BfArM), Germany, [4]NIAAA

To date, there have been a few large single and multi-site clinical trials in alcohol dependence conducted by the NIH (NIAAA) and Industry. While several medications (naltrexone and acamprosate) have been approved by the FDA in the last 20 years for this condition, wide-spread interest amongst pharmaceutical companies to develop medications for the treatment of alcohol dependence is lacking. Academics, NIAAA, the FDA in the US and EMA in Europe, as well as industry thought leaders agree that guidelines for drinking endpoints and consequences that define clinical success need better definition and consensus. Achieving this goal would reduce the regulatory risk involved with medication development for this condition, especially where markets for such medications are relatively undeveloped .In order to address this issue and others, the Alcohol Clinical Trials Initiative (ACTIVE) was formed several years ago with participation from expert academics, federal agencies (NIAAA, NIDA, FDA, and EMA) and the Pharmaceutical Industry (that has provided support for the effort). The overarching goal of this workgroup is to improve and standardize clinical trial methodologies for alcohol dependence. One very important mission of ACTIVE is to provide data that would inform a consensus around scientifically appropriate drinking outcome endpoints that would also have clinical meaning, and are acceptable to patients as well as healthcare providers and payers. Historically, in most treatment settings, abstinence from all alcohol has been the only acceptable goal. More recently, with the advent of anti-reinforcement medications, a goal of "no heavy drinking days" has been introduced. There is active discussion as to whether other drinking endpoints which might allow some heavy drinking days or some lesser reduction in drinking from pre-treatment levels might be appropriate and acceptable. In this panel, representatives from the FDA in the US and the EMA in Europe will share their current thinking on what could/should be considered acceptable drinking endpoints in clinical trials. Importantly, the FDA and EMA (influenced by the treatment cultures in which they operate) might not be strictly consistent in their approach to this issue and each could learn from the other. NIAAA has been vigorously working and supporting analyses of past clinical trial data sets to add new and informative information that might influence this discussion. Some of that data will be presented in this panel as well. The overarching goal of the panel is, with audience participation, to advance the thinking in this area. One big question that could be addressed is whether treatment providers are willing to consider a "paradigm shift" in this area and be willing to accept alcohol dependence as a chronic illness(similar to hypertension, diabetes, and obesity) that might require extended medication treatment but also allow a

reduction in harmful drinking to be considered as an endpoint of treatment, either by itself, or as an intermediate endpoint in a progression towards no harmful drinking or total abstinence. How one defines a reduction in harmful drinking is an important point to be considered in this discussion.

Learning Objectives:
- To better define what alcohol drinking endpoints for alcohol clinical trials are scientifically and clinically meaningful and acceptable.
- To acquaint the audience on the mission and accomplishments of the Alcohol Clinical Trials Initiative (ACTIVE) workgroup

INDIVIDUAL ABSTRACT:
FDA APPROACH TO CLINICAL TRIALS FOR ALCOHOLISM TREATMENT DRUGS
Celia Winchell, M.D.
Center for Drug Evaluation and Research, Food and Drug Administration
Clinical trials demonstrating direct clinical benefit of alcoholism treatment drugs might need to be very long and very large, and may be impractical. Therefore, drinking behavior observed during the brief window of a clinical trial serves as a surrogate endpoint. Conventional wisdom has long accepted the validity of sustained complete abstinence from drinking as a surrogate for clinical benefit. However, FDA has been interested for many years in identifying other patterns of drinking that are valid surrogates for clinical benefit. Based on analyses of data from clinical trial populations and longitudinal observational studies commissioned by NIAAA, we have permitted sponsors to design clinical trials that define as treatment responders those patients who reduce their drinking to non-problematic levels and sustain that pattern for a meaningful period of time. The current recommendation is for studies of 6 months' duration, with the primary endpoint being the proportion of patients who do not have any heavy drinking days from the end of a "grace period" to the end of the observation period (now called "PSNHDD"). We remain interested in learning whether other patterns of drinking can be validated as surrogates for clinical benefit.
 The origins of FDA's current recommendation will be discussed, along with the challenges of documenting and defining other types of reduction endpoints.

Learning Objectives:
- Understand the origins of the FDA's current approach to clinical trials for alcoholism treatment drugs.
- Recognize the challenges in documenting and defining various alternative endpoints.

Literature References:
- Medical Review of NDA 21-827
  http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021897s000_MedR_P1.pdf

INDIVIDUAL ABSTRACT:
CURRENT EUROPEAN REGULATORY PERSPECTIVE ON THE DEVELOPMENT OF MEDICATIONS FOR ALCOHOL USE DISORDERS
Michael Buehlen, M.D.
Federal Institute for Drugs and Medical Devices (BfArM), Germany
In September 2010, the European Medicines Agency (EMA) has released a Guideline on the development of medicinal products for the treatment of alcohol dependence. Based on current scientific knowledge, it is intended to provide the regulatory framework for the conduct of future

clinical trials in terms of valid treatment goals, study design, and clinically meaningful study endpoints.

In the light of addiction research the ultimate treatment goal in alcohol dependent patients is stable abstinence. Taking experiences made with already approved drugs like disulfiram, acamprosate or naltrexone into account, however, a clearly significant reduction in alcohol consumption with subsequent harm reduction is recognized as a valid treatment goal on the way to full abstinence.

Hence, two types of clinical studies may be conducted: 1) relapse prevention trials oriented at full abstinence demonstrated by the continued abstinence rate and 2) harm reduction studies. In the situation where the study is designed to focus on the intermediate goal of "clinically significant moderation in drinking", efficacy should be expressed by the following endpoints: change from baseline in total consumption of alcohol (per month, presented as amount of pure alcohol in grams per day) as well as by reduction in number of Heavy Drinking Days (HDD defined as more than 60 grams of pure alcohol in men and 40 grams in women). Both are considered primary variables, since HDD are associated with specific risks such as acute cardiovascular outcomes or accidents. A clinically relevant difference compared to placebo should be demonstrated. As the key secondary endpoint, efficacy should also be evaluated in terms of responders, reflecting an expected significant improvement in health outcome on an individual patient level. This could be done by evaluating the proportion of subjects with a 50%, 70% and 90% reduction in alcohol consumption, as well as the proportion of patients achieving stable abstinence. Another option would be evaluating the proportion of subjects with a significant (two-category) shift in WHO risk levels of drinking, i.e. proportion of patients who change from "very high risk" to "at least medium risk" level and/or change from "high risk to at least low risk".

Being the first issue of a European Regulatory Guideline directed at potential clinical trial sponsors in the field of Alcohol Dependence, ongoing clinical development may identify points that require further specification. Apart from providing an overview on the current EMA guideline provisions, the presentation will therefore also try to address issues that may require future regulation, like e.g. the need for clearly delineating target populations within the wide range of alcohol use disorders, handling of missing data in case of high withdrawal rates, or difficulties in demonstrating clinical relevance of treatment effects by combination of alcohol consumption reduction results with epidemiological data.

Learning Objectives:
- Familiarize with treatment goals and associated clinical study endpoints as currently acknowledged in Europe
- Identify issues within current European Guideline provisions that potentially deserve further specification

Literature References:
- Guideline on the development of medicinal products for the treatment of alcohol dependence, EMA/CHMP/EWP/20097/2008
- The Alcohol Clinical Trials Initiative (ACTIVE): Purpose and Goals for Assessing Important and Salient Issues for Medications Development in Alcohol Use Disorders. Neuropsychopharmacology (2012) 37,402-411

INDIVIDUAL ABSTRACT:
EXPLORATION OF ENDPOINTS FOR ALCOHOL CLINICAL TRIALS

Raye Z. Litten, III, Ph.D.
NIAAA
Determining a single or small set of standard, primary efficacy endpoints appropriate for alcohol clinical trials has been challenging. Recently, the Food and Drug Administration has designated percent subjects with no heavy drinking days (PSNHDD) as the primary endpoint for pivotal Phase 3 trials, while European Medicines Agency has designated reduction in heavy drinking and alcohol consumption. Since PSNHDD outcome measure has been used infrequently in previous alcohol clinical trials, the utility and validity of PSNHDD was evaluated in several data sets from multi-site alcohol clinical trials. In particular, PSNHDD effect sizes were compared to traditional treatment outcome measures, and various grace periods were explored. In addition, the relationship between frequency of heavy drinking and alcohol-related consequences was determined. Different cut-offs of heavy drinking days (HDD) as well as percent decreases in heavy drinking and alcohol consumption were determined using a cumulative responder analysis. Long-term outcome alcohol-related consequences, treatment utilization, and health care cost were determined in patients who exhibit no heavy drinking, low risk drinking, and heavy drinking during treatment. Limitations of these endpoints and next steps will be discussed.

Learning Objectives:
- To learn the various treatment endpoints used in alcohol clinical trials
- To learn new treatment endpoints being consider in future alcohol clinical trials

Literature References:
- Falk, D, X-Q Wang, L. Liu, J. Fertig, M. Mattson, M. Ryan, B. Johnson, R.Stout, and R.Z. Litten. Percentage of subjects with no heavy drinking days: Evaluation as an efficacy endpoint for alcohol clinical trials. Alcoholism: Clinical and Experimental Research, 34:2022-2034, 2010.
- Litten. R.Z., M. Egli, M. Heilig, C. Cui, J.B. Fertig, M.L. Ryan, D.E. Falk, H. Moss, R. Huebner, and A. Noronha. Medications development to treat alcohol use disorders: A vision for the next decade. Addiction Biology on line, 2012.

GENERAL DISCUSSION
Raymond F. Anton, M.D.
Medical University of South Carolina

PANEL
10:15 AM – 11:45 AM
PANEL OVERVIEW:
STUDYING SEXUAL DYSFUNCTION: HOW DO WE MANAGE CONFOUNDING FACTORS OF DISEASE STATE SYMPTOMS, PRIMARY DISORDER, AND MEDICATION ADVERSE EFFECTS?
Anita H. Clayton, M.D.[1], Phillip Kronstein, M.D.[2], Robert E. Pyke, M.D., Ph.D.[3], Ni Khin, M.D.[4]
[1]University of Virginia, Charlottesville[2] Division of Psychiatry Products/CDER/FDA, [3]S1 Biopharma, Inc., [4]Food and Drug Administration
Many factors contribute to sexual dysfunction in psychiatric patients including the presence of primary sexual disorders, as a symptom of a psychiatric illness, related to co-morbid conditions, and due to an adverse effect of medication. Separation of these issues in clinical practice and in clinical trials is difficult but necessary to determine appropriate management. To address the bidirectional relationship between these factors, Anita Clayton, MD will present 'Interaction of factors affecting sexual functioning.' Phillip Kronstein, MD will describe the 'Obstacles in

accurately assessing the impact of antidepressant medications on sexual function: Summary of findings from the FDA Forum on Measuring Sexual Dysfunction in Depression Trials.' How development of treatments for primary sexual disorders may be approached will be presented by Robert Pyke, MD, PhD in 'Optimizing the efficiency of early drug development for sexual dysfunction and the Lorexys Phase I-b/II-a experience.' Ni Khin, MD will discuss FDA Division of Psychiatry Products' current thinking on clinical trial design to evaluate and make potential labeling claims on sexual dysfunction.

Learning Objectives:
- Articulate the interaction of confounding factors that contribute to sexual dysfunction in psychiatric patients
- Determine when sexual dysfunction in psychiatric patients is a primary sexual disorder
- Describe current state-of-the-art in study design evaluating the effects of medications on sexual functioning

INDIVIDUAL ABSTRACT:
INTERACTION OF FACTORS AFFECTING SEXUAL FUNCTIONING
Anita H. Clayton, M.D.
Department of Psychiatry & Neurobehavioral Sciences, University of Virginia

Sexual functioning occurs via neuroendocrine systems. Excitatory hormones, peptides, and neurotransmitters include estrogen, testosterone, oxytocin, melanocortins, dopamine, norepinephrine, and nitric oxide; inhibitory effects occur with prolactin and serotonin. Psychiatric illness and the medications used to treat them also have effects on sexual functioning through these systems, making it difficult to separate the effect of the underlying condition from an adverse effect of treatment medications. Additionally, co-morbid psychiatric and medical conditions and associated medication use may confound assessment. In particular, there is a bidirectional relationship between primary sexual disorders like hypoactive sexual desire disorder and psychiatric conditions such as major depression. Methodological issues such as adequate quantitative measures of sexual functioning, statistical vs. clinically-meaningful differences, and gender effects may further complicate the picture. Current psychopharmacology research includes the search for an antidepressant without negative effects on sexual functioning, identification of antidotes for medication-induced sexual dysfunction, and treatments for primary sexual disorders in women and men.

Learning Objectives:
- Explain the overlap of neuroendocrine systems (hormones and neurotransmitters) associated with sexual dysfunction in primary sexual disorders, psychiatric illness, and psychotropic medication adverse effects.
- Describe the bidirectional relationships in sexual dysfunction between the disease state of major depression, primary sexual disorders, and medication side effects.
- Articulate methodological issues in the design of clinical trials in sexual dysfunction.

Literature References:
- Atlantis E and Sullivan T. Bidirectional association between depression and sexual dysfunction: A systemic review and meta-analysis. J Sex Med 2012;9:1497-1507.
- Clayton, AH, Keller A, McGarvey EL. Burden of Phase-Specific Sexual Dysfunction with SSRIs. Journal of Affective Disorders. 91:27-32, 2006.
- Clayton, AH, Hamilton, DV. Female Sexual Dysfunction. *Psychiatric Clinics of North America.* 33:323-338, 2010

INDIVIDUAL ABSTRACT:
SUMMARY OF FINDINGS FROM FDA REGULATORY SCIENCE FORUM ON MEASURING SEXUAL DYSFUNCTION IN DEPRESSION TRIALS

Phillip Kronstein, M.D.
Division of Psychiatry Products/CDER/FDA

Sexual dysfunction (SD) is an important treatment-emergent adverse effect of antidepressant treatment that can interfere with treatment compliance. This problem appears to be more prominent for particular classes of antidepressants, namely the selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). However, the rates of SD are often underestimated and underreported in the clinical trials supporting drug approval. To address this issue, the FDA's Division of Psychiatry Products (DPP) recently held a Regulatory Science Forum, including expert clinicians from academia and some industry representatives, titled "Measuring Sexual Dysfunction in Depression Trials." This presentation will briefly summarize the two key FDA presentations for the forum: (1) The results of our literature search to look at the rates of SD with SSRIs and SNRIs; (2) Exploratory analyses of short-term monotherapy trials for major depressive disorder included in NDA submissions that utilized either of two standardized instruments to assess sexual dysfunction, the Changes in Sexual Functioning Questionnaire (CSFQ-14) or the Arizona Sexual Experience (ASEX) scale. The advantages and limitations of these two scales, based on our literature search and exploratory analyses of NDA submissions, will be discussed.

Learning Objectives:
- To identify the rates of sexual dysfunction with SSRIs and SNRIs
- To understand the advantages and limitations of using different scales and methods to assess sexual dysfunction in depression trials

Literature References:
- Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009 Jun;29(3):259-66
- Coleman CC, Cunningham LA, Foster VJ, Batey SR, Donahue RM, Houser TL, Ascher JA. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry 1999; 11:205-15
- Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, Modell JG: Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. *J Clin Psychiatry* 2006; 67:736-46.
  Delgado PL, Brannan SK, Mallinckrodt CH, Tran PV, McNamara RK, Wang F, Watkin JG, Detke MJ: Sexual functioning assessed in 4 double-blind placebo- and paroxetine-controlled trials of duloxetine for major depressive disorder. *J Clin Psychiatry 2005*; 66:686-92

INDIVIDUAL ABSTRACT:
OPTIMIZING THE EFFICIENCY OF EARLY DRUG DEVELOPMENT FOR SEXUAL DYSFUNCTION AND THE LOREXYS PHASE I-B/II-A EXPERIENCE

Robert E. Pyke, M.D., Ph.D.
S1 Biopharma, Inc.

Background: Clinical development of agents to treat sexual dysfunction is increasingly becoming the province of fledgling pharma companies. For start-ups, clinical feasibility data are vital to propel drug development and attract capital. Yet, inadequate early studies of dose response can stall the process. Phase I-b is little used for this. Phase II-a has been used with little control or, more recently by big pharma, bypassed to rely on large proof-of-concept studies. **Methods:** Phase I-b and II-a designs are combined for more efficient and predictive early testing of Lorexys® (pat. pend.) for Hypoactive Sexual Desire Disorder. To optimize power and minimize n, measures sensitive to change assure adequate severity, and newer statistical tools including MMRM replace old standards. Crossover treatments test response; washouts are based on known PK/PD. A set of a few subjects is exposed to three open-label treatments: control; lowest dose of test agent predicted to have activity; and dose of test agent predicted for mid-range of activity. An expert committee decides the next doses. Ratings of treatment are done remotely to minimize placebo effect.
Results/Conclusion: Careful planning should increase the efficiency of early drug development. Results with Lorexys® will contribute to this methodology

Learning Objectives:
- Describe current state-of-the-art in study design evaluating the effects of medications on sexual functioning
- Describe results with Lorexys (R)
- none

Literature References:
- Moll JL, Brown CS, The use of monamine pharmacologic agents in the treatment of sexual dysfunction: evidence in the literature, J Sex Med 2011;8:956-970.
- Background Document, NDA 22-526 Flibanserin for hypoactive sexual desire disorder in premenopausal women, FDA May 20, 2010 http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM215437.pdf
- none

GENERAL DISCUSSION
Ni Khin, M.D.
Food and Drug Administration

WORKSHOP
2:00 PM – 5:00 PM
WORKSHOP OVERVIEW:
ADVANCING TREATMENT DISCOVERY IN MAJOR DEPRESSION: KETAMINE AND OTHER NOVEL ANTIDEPRESSANT APPROACHES
James W. Murrough, M.D.[1], Giacomo Salvadore, M.D.[2], Maura Furey, Ph.D.[3], Dan V. Iosifescu, M.D., M.Sc.[1], Charles H. Kellner, M.D.[1], Sanjay J. Mathew, M.D.[4]
[1]Mount Sinai School of Medicine, [2]Janssen Pharmaceuticals, [3]Experimental Therapeutics and Pathophysiology Branch/NIMH, [4]Michael E Debakey VA Medical Center, Houston, TX; Baylor College of Medicine
Up to two-thirds of patients with major depressive disorder (MDD) will remain ill despite an optimized trial of an antidepressant [e.g. they suffer from treatment-resistant depression (TRD)], and response is slow even in patients who eventually derive benefit. The rapid antidepressant effect found associated with the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist

ketamine, even in TRD, has spurred clinical and translational research aimed at developing ketamine's therapeutic potential and elucidating the underlying mechanism of antidepressant action. The demonstration that rapid antidepressant effects are now achievable has opened the door to search for other interventions that also act rapidly and to understand the neurobiology underlying rapid treatment response. New efficacy and safety data from a two-site, randomized, parallel-arm, midazolam-controlled, clinical trial of ketamine in TRD (n=72) will be presented as well as recent findings from human biomarker studies of ketamine in depression utilizing MEG and magnetic resonance (MR)-based techniques. Beyond ketamine, the antidepressant potential of the antimuscarinic agent scopolamine will be discussed, as well as the results of recent biomarker studies. New data will be presented on the therapeutic effects of minocyline – a glutamate modulator with antioxidant and neurotrophic effects – in bipolar depression. New data from multi-center trials of electroconvulsive therapy (ECT) will be presented that suggest some patients manifest a rapid antidepressant response to ECT. The symposium will conclude with a discussion on the current state of new and potentially fast-acting antidepressant interventions, existing challenges and future directions.

Learning Objectives:
- To incorporate recent advances into our understanding of the clinical response to ketamine, scopolamine, minocyline and ECT in major depression
- To understand recent advances in characterizing neural biomarkers of rapid antidepressant response in major depression

INDIVIDUAL ABSTRACT:
ANTIDEPRESSANT EFFICACY OF KETAMINE IN TREATMENT-RESISTANT MAJOR DEPRESSION: A TWO-SITE, RANDOMIZED, PARALLEL-ARM, MIDAZOLAM-CONTROLLED, CLINICAL TRIAL
James W. Murrough, M.D.
Mount Sinai School of Medicine

Background: Several small, single-site studies have suggested that ketamine has rapid antidepressant effects. Previous trials of ketamine, however, have utilized crossover designs with saline as a control condition thereby limiting the interpretation of these studies. The current study was designed to address these limitations in order to more definitely characterize the antidepressant effects of ketamine.

Methods: 72 patients with treatment-resistant major depression (TRD) received a single 40-minute IV infusion of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) in a 2:1 randomization scheme. The primary outcome was change in MADRS score from baseline to 24 hours post-infusion and proportion of participants meeting response criteria at 24 hours, defined as $\geq$ 50% reduction in MADRS score.

Results: After controlling for site differences, treatment, and time, a treatment x time interaction demonstrated differential change for the two groups over the first 24 hour period ($F_{(1,70)} = 9.62$, $p < 0.003$). Ketamine demonstrated a 16.5 point decrease ($t(46) = -10.31$, $p < 0.0001$) on the MADRS while midazolam showed an 8.8 point decrease ($t(24) = -4.63$, $p < 0.0001$). At 24 hours post-infusion, the response rate in the ketamine arm was 63.8%, compared to 28.0% in the midazolam arm (p=0.006).

Conclusion: In the largest clinical trial testing the efficacy of IV ketamine in mood disorders conducted to date, ketamine was associated with a rapid and large antidepressant effect at 24

hours, significantly superior to midazolam. Ketamine appears to possess rapid antidepressant effects independent of its transient psychoactive effects.

Learning Objectives:
- To understand the current evidence base for the efficacy of ketamine for treatment-resistant depression
- To understand what is currently known regarding the safety and tolerability of ketamine for treatment-resistant depression

Literature References:
- Zarate CA Jr, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006; 63(8): 856-64.
- Murrough JW, et al. Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression. Biol Psychiatry. 2012 [Epub ahead of print]

INDIVIDUAL ABSTRACT:
KETAMINE BIOMARKERS IN DEPRESSION: PROMISING SCIENCE AND ANSWERED QUESTIONS
Giacomo Salvadore, M.D.
Janssen Pharmaceuticals

The finding that the NMDA antagonist ketamine exerts rapid onset of antidepressant effects in patients with treatment refractory mood disorders has fueled tremendous efforts in trying to understand the mechanism underlying ketamine's antidepressant properties via downstream targets of NMDA blockade (i.e., pharmacodynamic biomarkers). Furthermore, ketamine also represents an ideal "tool" compound to discover novel biomarkers to identify more homogenous group of patients who would mostly benefit from drugs with a glutamatergic mechanism of action (i.e., response biomarkers).

Promising techniques which have been used to investigate pharmacodynamic and response biomarkers of ketamine treatment include magnetoencephalography, magnetic resonance spectroscopy, fMRI and EEG. For example, we recently used somatosensory evoked fields to investigate brain plasticity in depressed patients who received subanesthetic ketamine. We showed that ketamine responders displayed increased somatosensory evoked fields gamma power 6-7 hours post-ketamine, while this effect was not present in non-responders.Studies which investigated response biomarkers to ketamine showed that responders seem to be characterized by higher activity in the pregenual anterior cingulate cortex when exposed to affectively charged stimuli and also by lower levels of glutamine in the dorsal prefrontal cortex. However, much of this evidence comes out of small uncontrolled studies and it is unknown whether those putative biomarkers are specific to drugs which target the glutamatergic system. Another unanswered question involves the time course of biomarker changes induced by ketamine administration, i.e. which effects precede and which one parallel the clinical improvement observed in patients with mood disorders. Here we will review human biomarker studies of ketamine with an emphasis on translational approaches; current limitations and future directions for this important line of research will be addressed as well.

Learning Objectives:
- To understand current knowledge about the mechanism of action of ketamine in depression.

- To understand translational approaches to investigate pharmacodynamic biomarkers of ketamine in depression
- To understand the critical knowledge gaps about the use of ketamine in depression and future directions for the investigation of ketamine as a promising tool to develop novel more effective and fast acting antidepressants.

Literature References:
- Cornwell B, Salvadore G et al., 2012. Synaptic potentiation is critical for rapid antidepressant response to ketamine in treatment-resistant major depression. Biol Psychiatry. 2012 Oct 1;72(7):555-61
- Salvadore G, van der Veen JW, Zhang Y, Marenco S, Machado-Vieira R, Baumann J, Ibrahim LA, Luckenbaugh DA, Shen J, Drevets WC, Zarate CA Jr. An investigation of amino-acid neurotransmitters as potential predictors of clinical improvement to ketamine in depression.Int J Neuropsychopharmacol. 2012 Sep;15(8):1063-72.

INDIVIDUAL ABSTRACT:
RAPID ANTIDEPRESSANT EFFECTS AND BIOMARKERS OF CLINICAL RESPONSE TO SCOPOLAMINE
Maura Furey, Ph.D.
Experimental Therapeutics and Pathophysiology Branch/NIMH

Background: Cholinergic muscarinic receptors are hyper-responsive in mood disorders and the antimuscarinic scopolamine produces rapid antidepressant effects. Acetylcholine also is important in stimulus processing and the hyper-responsive cholinergic system may account for stimulus processing biases in mood disorders. Here we present new results characterizing biomarkers of antidepressant response to scopolamine related to stimulus processing biases.
Methods: Depressed MDD patients (n=16) participated in a functional magnetic resonance imaging study followed by a double-blind, placebo-controlled i.v. scopolamine (4ug/kg) trial. During task, two images of superimposed faces (happy/sad) and houses were presented. Participants attended to faces (AF) or houses (AH) and performed a matching task. Multiple regression estimated BOLD response during AF and AH when expressions were sad (AFs, AHs) and happy (AFh, AHh). The difference in BOLD signal during explicit (AFh-AFs) and implicit (AHh-AHs) processing was correlated with percent change in MADRS following treatment (voxel p<0.005; WBC p<0.05).
Results: No change in MADRS was observed during placebo (p> 0.20); reductions occurred following scopolamine (p<0.001). During implicit processing, the difference in BOLD signal (AHh-AHs) correlated positively with treatment outcome in the ACC and correlated negatively in middle occipital cortex (p< 0.05). No correlation occurred during explicit processing.
Conclusions: Baseline differences in the implicit emotion processing of faces may provide a biomarker of treatment response to scopolamine. The results may suggest that the level of baseline cholinergic dysfunction is evident in patterns of response to emotional stimuli, and that the extent of dysfunction predicts the magnitude of subsequent treatment response.

Learning Objectives:
- To understand the clinical response to scopolamine in the treatment of mood disorders.
- To characterize neural biomarkers of antidepressant response to scopolamine

Literature References:
- Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. Arch Gen Psychiatry 2006; 63: 1121-9.

- Furey, M.L., Drevets, W.C., Hoffman, E.M., Frankel. E., Speer, A.M., Zarate, C.A. Jr. Pre-treatment neural activity in visual cortex during emotional processing predicts treatment response to scopolamine in major depressive disorder. Archives of General Psychiatry, in press.

INDIVIDUAL ABSTRACT:
THE EFFICACY OF MINOCYCLINE FOR BIPOLAR DEPRESSION AND ITS IMPACT ON GLUTAMATERGIC AND ANTIOXIDANT METABOLITES
Dan V. Iosifescu, M.D., M.Sc.
Mount Sinai School of Medicine

Background: Bipolar depression is the largest unmet need in the treatment of bipolar disorder. Minocycline, an antibiotic used for several decades, appears to have multiple mechanisms potentially relevant to the pathophysiology of bipolar disorder: modulation of glutamate neurotransmission, anti-inflammatory, antioxidant and neuroprotective effects. Several animal studies have reported antidepressant-like effects of minocycline, alone or in combination with glutamate antagonists, in the forced swim test and in the learned helplessness models. We tested here whether minocycline added to mood stabilizers can be an effective treatment for acute bipolar depression.

Method: N=12 subjects with bipolar disorder type I (75% males, mean age 44.4 ± 3.2 years) experiencing acute major depressive episodes started an 8-week, open study with adjuvant minocycline (100-300 mg) added to their current mood stabilizing treatment. We administered depression severity scales (MADRS) and CGI every two weeks. We collected proton magnetic resonance spectroscopy (1H-MRS) from N=7 patients before and after treatment (from two 2.5x2.5x3-cm3 voxels, one centered on ACC, the other placed in the occipital cortex) to detect changes in glutamate-glutamine (Glx) and in glutathione (GSH), an important brain antioxidant molecule in the brain, during the 8-week treatment.

Results: Of the first 9 subjects completing the 8 week treatment, MADRS scores decreased from 27.5 ± 4.0 at baseline to 13.6 ± 10.6 at endpoint (p=0.007). 67% of subjects were treatment responders (≥ 50% reduction in MADRS scores from baseline) and 45% achieved remission (defined as endpoint MADRS ≤ 10). Minocycline-treated subjects (N=7) had significant decreases in the combined glutamate-glutamine (Glx) levels (20.9% decrease, p=0.017) in the ACC from baseline to endpoint (week 8). Occipital GSH increased non-significantly 6.8% from baseline (p=NS). Additional data from this on-going study will be presented at the meeting.

Conclusion: Minocycline may be an effective adjuvant treatment for bipolar depression. Preliminary MRS results are consistent with the hypothesized role of minocycline in reducing excessive glutamate and glutamate-mediated excitotoxicity in brain areas involved in mood regulation. A full-scale clinical trial to assess the antidepressant efficacy of minocycline is warranted.

Learning Objectives:
- Understand the effects of minocycline on glutamate neurotransmission, and its anti-inflammatory, antioxidant and neuroprotective effects.
- Review the roles of these mechanisms (glutamate excitotoxicity, inflammation, oxidative stress) in the pathology of bipolar disorder
- Describe the antidepressant efficacy of minocycline in animal models and its preliminary efficacy in bipolar depression

Literature References:

- Dean OM, Data-Franco J, Giorlando F, Berk M. Minocycline: therapeutic potential in psychiatry. CNS Drugs. 2012; 26(5):391-401.
- Molina-Hernandez M, Tellez-Alcantara NP, Perez-Garcia J, Olivera-Lopez JI, Jaramillo-Jaimes MT. Antidepressant-like actions of minocycline combined with several glutamate antagonists. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(2):380-6.

INDIVIDUAL ABSTRACT:
SPEED OF RESPONSE TO ECT: REDISCOVERING THE GOLD STANDARD
Charles H. Kellner, M.D.
Mount Sinai School of Medicine
While electroconvulsive therapy (ECT) is widely recognized as the most effective acute antidepressant treatment, its speed of response has received comparatively little attention. In fact, ECT is a rapidly acting treatment, typically leading to remission in severely ill, medication-refractory patients within approximately 2 weeks. A subset of patients responds even more quickly, with remission in the first week. Even more remarkable is the fact that, for many patients, there is a substantial drop in depression rating scale scores immediately after the first ECT. In this presentation, we review data from two NIMH-supported multi-center trials of ECT, in which acutely depressed patients were rated with the 24-item Hamilton Rating Scale for Depression (HAM-D-24) at baseline and before each subsequent ECT. These data demonstrate the favorable time course of response with ECT. They also show that the first ECT in a series often has a dramatic, immediate influence on depression rating scores. This improvement was seen with all three electrode placements, even when administered at low stimulus doses, during the initial dose titration session (to determine seizure threshold [ST]). Such data call into question the long-held belief that low-dose right unilateral (RUL) ECT is a weak antidepressant treatment. We will discuss the implications of these findings for optimizing treatment strategies for seriously ill patients, for whom ECT remains an important treatment modality

Learning Objectives:
- To understand that the speed of response to ECT compares very favorably to that of typical antidepressant medications.
- To understand that the first ECT in a series often confers substantial antidepressant effect.

Literature References:
- Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, Biggs MM, O'Connor K, Rasmussen K, Litle M, Zhao W, Bernstein HJ, Smith G, Mueller M, McClintock SM, Bailine SH, Kellner CH. J Clin Psychiatry. 2004 Apr;65(4):485-91.
- Effect of the first electroconvulsive therapy in a series. Kellner CH, Knapp RG. J ECT. 2007 Sep;23(3):208.

GENERAL DISCUSSION
Sanjay J. Mathew, M.D.
Michael E Debakey VA Medical Center, Houston, TX; Baylor College of Medicine

WORKSHOP
2:00 PM – 5:00 PM

WORKSHOP OVERVIEW:
IMPEDIMENTS/BARRIERS TO EFFECTIVE TEACHING-LEARNING OF PSYCHOPHARMACOLOGY

Marlene P. Freeman, M.D.[1], Leslie Citrome, M.D., MPH[2], Ira Glick, M.D.[3], J.P. Lindenmayer, M.D.[4]

[1]Harvard Medical School, Massachusetts General Hospital, [2]New York Medical College, [3]Stanford University School of Medicine, [4]New York University School of Medicine

This workshop will examine the teaching and learning of clinical psychopharmacology for medical students, residents and psychopharmacology providers. The focus is on the impediments and possible solutions to include learning and ultimately clinical practice. Dr. Lindenmayer will describe common clinical practice patterns, asking the question whether, knowing the "literature matters?" Dr. Citrome will describe the new electronic tools (organizing the literature) and how this can be integrated into teaching resources. Dr. Marlene Freeman will speak on barriers to teaching psychopharmacology (in and out of class) to residents and medical students. Finally, Dr. Glick and Dr. Salzman will cover issues related to psychopharmacology teachers as they work "the 7 sins of teaching."

Learning Objectives:
- Innovate technology techniques to improve the learning for clinical psychology in order to improve practice.
- Identify the impediments to the psychopharmacology teaching-learning process.

INDIVIDUAL ABSTRACT:
THE SEVEN SINS OF PSYCHOPHARMACOLOGY TEACHING

Ira Glick, M.D.
Stanford University School of Medicine

This presentation focuses on what psychopharmacology teachers do or don't teach. These "sins" include such issues as forgetting to discuss (1) dosing and duration of treatment, (2) clinical context of a patient's life, (3) shared decision making, (4) the full-range of drugs in a class, (5) what can be expected in terms of outcome from a particular drug class and (6) when to include family/significant others in treatment. A final issue is not evaluating basic clinical competence of a trainee or student.

Literature References:
- Glick, I., Balon, R., & Citrome, L. (2010). ASCP Model Psychopharmacology Curriculum for Training Directors and Teachers of Psychopharmacology in Psychiatric Residency Programs (6th ed.). Retrieved from http://psychopharmcurriculum.com
- Glick, I., Balon, R., & Citrome, L. (2012). ASCP Model Psychopharmacology Curriculum for Training Directors and Teachers of Psychopharmacology in Psychiatric Residency Programs (7th ed.). Retrieved from http://psychopharmcurriculum.com

INDIVIDUAL ABSTRACT:
BARRIERS TO TEACHING PSYCHOPHARMACOLOGY TO RESIDENTS AND MEDICAL STUDENTS

Marlene P. Freeman, M.D.
Harvard Medical School, Massachusetts General Hospital

In this presentation, the focus will be barriers to teaching psychopharmacology to residents and medical students. We will discuss individual, environmental, and logistical hurdles that make

teaching psychopharmacology challenging, and have an interactive discussion about overcoming these barriers. Challenging teaching situations will include teaching medical students with broad interests outside of psychiatry, the overwhelmed junior resident who is managing acutely and severely ill patients in crisis and inpatient settings, and the senior residents who are getting ready to move on from training.

Learning Objectives:
- To discuss challenges in teaching residents psychopharmacology.
- To discuss challenges in teaching medical students interested in a variety of disciplines psychopharmacology.

Literature References:
- Zisook et al., Teaching psychopharmacology: what works and what doesn't. J Clin Psychopharmacol. 2008 Feb;28(1):96-100.
- Kane et al., New Clinical Drug Evaluation Unit (NCDEU) annual meeting: a great opportunity for early career psychiatrists. J Clin Psychiatry. 2012 Apr;73(4):504-5.

INDIVIDUAL ABSTRACT:
INPATIENT PSYCHOPHARMACOLOGY IN TEACHING HOSPITALS: THE GOOD NEWS AND THE BAD NEWS
J.P. Lindenmayer, M.D.
New York University School of Medicine
This presentation will address the current status of inpatient psychopharmacology in a number of NYC teaching hospitals and compare the observed patterns to published practice guidelines. The data was collected during a period of 6 months from medical records of patients referred to a tertiary care setting for long term treatment in the context of suboptimal response in the shorter term inpatient setting. The following medication patterns were reviewed: use of adequate dose levels, use of second generation antipsychotics, use of depot formulations in patients with impaired compliance, use of clozapine, use of polypharmacy and monitoring of plasma levels. Results indicate that increasingly first generation antipsychotics are reappearing, that dose levels tend to be suboptimal and do not follow published results of RCTs, that clozapine use is minimal and that plasma level monitoring is rare resulting overall in modest compliance with published practice guidelines and results from RCTs. The good news is that aspects of these practice patterns can be modified with feedback to clinicians based on published data and peer counseling. An example is presented on the increase of clozapine usage after this intervention.

Learning Objectives:
- After this presentation the audience will understand the type of suboptimal psychopharmacological practice patterns found in inpatient teaching hospitals.
- After this presentation the audience will have observed the effectiveness of an intervention designed to enhance the usage of clozapine in shorter term inpatient settings.

Literature References:
- Practice guideline for the treatment of patients with schizophrenia, second edition.Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J; American Psychiatric Association; Steering Committee on Practice Guidelines. Am J Psychiatry. 2004 Feb;161(2 Suppl):1-56.
- The International Psychopharmacology Algorithm Project (IPAP; http://www.ipap.org)

INDIVIDUAL ABSTRACT:

YOU HAVE SEARCHED, YOU HAVE FOUND, NOW WHAT? GOING DIGITAL AND BUILDING AN ELECTRONIC LIBRARY
Leslie Citrome, M.D., MPH
New York Medical College
In addition to manual searching of information in printed journals and on-line, we now have the availability of automated delivery of articles that meet our pre-specified areas of interest. The quantity of information exceeds our printing capabilities but is easily accommodated electronically. Searching our electronic libraries is made easier with free software tools. The next step is to transform legacy information sources (our printed journals, article libraries and books) into digital format. For journals this may not be necessary for persons with remote access to university libraries, but for books this ought to be seriously considered and will allow the searching of text across all books in one's possession. Methods of information storage, indexing, backup, retrieval, viewing and sharing are briefly reviewed, followed by a step-by-step guide to converting hard and soft-cover books to PDF format using guillotine cutters that can slice through 3 inches of a bound book and scanning the resultant sheets of paper using relatively inexpensive but rapid (40-80 pages/minute) sheet-fed scanners.

Learning Objectives:
- Increase knowledge and competence in dealing with adverse effects of clozapine
- Incorporate knowledge about management strategies into clinical care
- Be able to convert journal articles, books and other printed materials into digital format
  Help eliminate file cabinets full of paper and bookshelves full of books that your heirs will throw out when you die anyway

Literature References:
- Citrome L, Moss SV, Graf C. How to search and harvest the medical literature: let the citations come to you, and how to proceed when they do. Int J Clin Pract. 2009 Nov;63(11):1565-70
- Citrome L. Creating a more productive, clutter-free, paperless office: a primer on scanning, storage and searching of PDF documents on personal computers. Int J Clin Pract. 2008 Mar;62(3):363-6.
- Citrome L, Moss SV. How to efficiently maintain your own electronic resource library. J Clin Psychiatry. 2010 Feb;71(2):207-8.

WORKSHOP
2:00 PM – 5:00 PM
WORKSHOP OVERVIEW:
PLACEBO RESPONSE IN ANTIDEPRESSANT CLINICAL TRIALS: PATIENT CHARACTERISTICS, STUDY DESIGN FEATURES, AND DATA ANALYTIC TECHNIQUES
Bret R. Rutherford, M.D.[1], Steven Roose, M.D.[2], Michael E. Thase, M.D.[3], Craig Nelson, M.D.[4]
[1]Columbia University College of Physicians and Surgeons, [2]Columbia University, [3]Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center, [4]University of California San Francsico
Placebo response in clinical trials of antidepressant medications is substantial and increasing. High placebo response rates hamper efforts to detect signals of efficacy for new antidepressant medications, contributing to more failed trials and delaying the delivery of new treatments to market. Media reports seize upon increasing placebo response and modest advantages for active

drugs as reasons to question the value of antidepressant medication, which may further stigmatize treatments for depression and dissuade patients from accessing mental health care. Conversely, enhancing the factors responsible for placebo response may represent a strategy for improving available treatments for Major Depressive Disorder. The purpose of this workshop is to review and synthesize recent research on the mechanisms of placebo effects in antidepressant clinical trials and the study design features mediating and moderating their magnitude. Of particular interest will be generating a discussion between speakers and audience members about what this research suggests about helpful avenues to minimize placebo response in clinical trials and maximize clinical outcomes in community practice.

First, Dr. Bret Rutherford will present a conceptual framework describing the sources of placebo response in antidepressant clinical trials. Next, Dr. Craig Nelson will present the results of meta-analyses which identify clinical and demographic features of patients that predict increased rates of placebo response. Dr. Steven Roose will report on the results of a series of analyses identifying clinical trial design features that are associated with placebo response, particularly those design features which influence patient expectancy. Dr. Michael Thase will discuss limitations of standard data analyses in antidepressant trials and propose new strategies to improve signal detection. A discussion with audience participation will follow to generate strategies of reducing placebo response in the drug development setting, and it will be asked whether the optimal strategy in clinical practice may be to enhance the factors giving rise to placebo response in order to improve treatment outcome.

Learning Objectives:
- After participating in this workshop, attendees will be able to enumerate three primary sources of placebo response in antidepressant clinical trials.
- After participating in this workshop, attendees will be able to identify five study design features that influence placebo response in antidepressant clinical trials.
- After participating in this workshop, attendees will be able to discuss two methods of analyzing outcome data from clinical trials with their attendant strengths and weaknesses for signal detection.

INDIVIDUAL ABSTRACT:
A MODEL OF PLACEBO RESPONSE IN ANTIDEPRESSANT CLINICAL TRIALS
Bret R. Rutherford, M.D.
Columbia University College of Physicians and Surgeons

Placebo response in clinical trials of antidepressant medications is substantial and increasing. High placebo response rates hamper efforts to detect signals of efficacy for new antidepressant medications, contributing to more failed trials and delaying the delivery of new treatments to market. Media reports seize upon increasing placebo response and modest advantages for active drugs as reasons to question the value of antidepressant medication, which may further stigmatize treatments for depression and dissuade patients from accessing mental health care. Conversely, enhancing the factors responsible for placebo response may represent a strategy for improving available treatments for Major Depressive Disorder. A conceptual framework describing the causes of placebo response is needed in order to develop strategies for minimizing placebo response in clinical trials, maximizing placebo response in clinical practice, and talking with depressed patients about the risks and benefits of antidepressant medications. This review examines contributors to placebo response in antidepressant clinical trials and proposes an explanatory model. Research aimed at reducing placebo response should focus on limiting

patient expectancy and the intensity of therapeutic contact in antidepressant clinical trials, while the optimal strategy in clinical practice may be to combine active medication with a presentation and level of therapeutic contact that enhances treatment response.

Learning Objectives:
- At the end of this presentation, participants will be able to distinguish the terms placebo effect and placebo response and discuss the relevance of each for clinical trials and open clinical treatment.
- At the end of this presentation, participants will be able to distinguish the terms placebo effect and placebo response and discuss the relevance of each for clinical trials and open clinical treatment.

Literature References:
- Rutherford BR, Roose SP. A Model of Placebo Response in Antidepressant Clinical Trials. In Press, Am J Psychiatry.
- Rutherford BR, Sneed JR, Tandler J, Peterson BS, Roose SP. Deconstructing Pediatric Depression Trials: An Analysis of the Effects of Expectancy and Therapeutic Contact. J Am Acad Child Adolesc Psychiatry 2011; 50:782-795.

INDIVIDUAL ABSTRACT:
PREDICTORS OF PLACEBO RESPONSE IN DEPRESSION
Craig Nelson, M.D.
University of California San Francsico

Placebo response plays an important role in depression treatment. Depending on your aim it may be advantageous to promote or restrict placebo response. The objective of the current study was to identify predictors of placebo remission. Those predictors might be used to subtype patients as 'placebo remitters' or 'placebo non-remitters.' A possible application will be presented. This was a retrospective analysis of 11 placebo controlled duloxetine trials. A total of 1017 patients with MDD and baseline Hamilton Depression rating scale (HAMD) scores $\geq$15 received placebo and were included. Remission was defined as HAMD $\leq$ 7 at endpoint (7–8 weeks). The sample was split into training data (N=813, 80%) for model selection and test data (N=204, 20%) for validation. Forty-five variables were tested as potential predictors. Logistic regression and classification and regression tree (CART) methods were used to identify predictors of remission. Models were first derived in the completer sample but also examined in the modified ITT sample using LOCF. Predictive accuracy of models was assessed by Receiver Operator Characteristic (ROC) curves.The optimal logistic regression model included four variables—age, core depression severity (HAMD items 1, 2, 3, 7, 8), HAMD anxiety/somatization scale, and duration of episode. In the test sample the predictive value was modest, 0.63 (the AUC of the ROC). The CART method used essentially the same four variables but in addition determined an order (most predictive) and an optimal threshold. Patients likely to remit (40% probability) were those under age 34, or episode duration $\geq$ 12 weeks and A/S factor < 7 and HAMD core subscale < 8, or episode duration < 12 weeks and age < 53 years. The predictive value of the CART model was lower, 0.57. As a potential use of the predictor model, the variables in the CART model with their thresholds were applied in 7 trials that included duloxetine, a SSRI, and placebo to identify subgroups of likely placebo remitters and likely placebo non-remitters. As predicted, drug placebo differences were greater in patients identified as placebo non-remitters than in those labeled placebo remitters. The potential implications of these data will be discussed.

Learning Objectives:

- Recognize possible predictors of placebo response
- Describe potential applications of the predictor models

Literature References:
- Nelson JC, Zhang Q, Deberdt W, Marangell LB, Karamustafalioglu O, Lipkovich IA. Predictors of remission with placebo using an integrated study database from patients with major depressive disorder. Curr Med Res Opin 2012;28(3):325-34.
- Alexopoulos GS, Kanellopoulos D, Murphy C, et al. Placebo response and antidepressant response. Am J Geriatr Psychiatry. 2007 Feb;15(2):149-58.

INDIVIDUAL ABSTRACT:
EVIDENCE THAT STUDY DESIGN IMPACTS RESPONSE RATES IN ANTIDEPRESSANT CLINICAL TRIALS

Steven Roose, M.D.
Columbia University

Clinical trial study design influences response rates to placebo as well as active medication. For example, an increasing likelihood of receiving active medication as opposed to placebo appears to increase response rates. A series of meta-analyses performed by our research group in three different patient samples (pediatric, adult, and late life) have analyzed antidepressant response in comparator (i.e., medication vs. medication) antidepressant trials vs. placebo-controlled trials. Patients in comparator trials know they are receiving a medication without knowing the exact agent, while patients in placebo-controlled trials do not know whether they are receiving an active medication. This disparate knowledge may contribute to an increased expectancy of improvement among participants in comparator studies, and greater expectancy of improvement has been linked to the improvement of depressive symptoms in clinical trials. In 48 placebo-controlled and 42 comparator trials enrolling depressed adults aged 18-65, the odds of being classified as a responder to medication in comparator trials were 1.8 times the odds of being classified as a responder in placebo-controlled trials (95% CI = 1.45 - 2.17, p < 0.001), and the odds of being classified as a remitter to medication in comparator trials were 1.5 times the odds of being classified as a remitter in placebo-controlled trials (95% CI = 1.11 - 2.11, p < 0.001). Similarly, in a sample of patients with late life depression, the odds of being classified a responder in comparator trials were nearly two times the odds of responding in the placebo-controlled trials and the estimated probability of response in placebo-controlled trials was 0.46 compared to 0.63 in comparator trials. However, no such differences were found in a meta-analysis of medication response in placebo-controlled and comparator studies for pediatric depression. It appears children and adolescents do not generate the same treatment expectancies as do adult RCT participants, and consequently differences in patient expectancy do not cause differential medication response rates across study designs. Younger patients entering clinical studies may not receive the same information disclosure as adults and may not be as cognitively capable of understanding what information they do receive. After reviewing these data, the significance of these findings will be discussed for the design of clinical trials, the practice of evidence based medicine, and in particular the design of studies comparing psychotherapy with medication.

Learning Objectives:
- To review the evidence that study design impacts response rates in antidepressant clinical trials
- To discuss the role of patient expectancy in placebo response

Literature References:
- Rutherford BR, Sneed JR, Roose SP. Does Study Design Affect Outcome? The Effects of Placebo Control and Treatment Duration in Antidepressant Trials, Psychotherapy and Psychosomatics. 2009, 78:172-181.
- Sneed JR, Rutherford BR, Rindskopf D, Roose SP. Design Makes a Difference: Antidepressant Response Rates in Placebo-controlled versus Comparator Trials in Late Life Depression. Am J Geri Psychiatry. 2008, 16:65-73.

INDIVIDUAL ABSTRACT:
ARE RELATIVELY SMALL EFFECT SIZES IN RCTS SYNOMOUS WITH TRIVIAL BENEFITS FOR DEPRESSED PATIENTS?

Michael E. Thase, M.D.
Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center

Across the past three decades, the magnitude of the placebo response in randomized controlled trials (RCTs) of antidepressants has nearly doubled and, as a result, the specific effect size of antidepressant therapy has decreased proportionally. As a result, the mean effect size for most widely used modern antidepressants is on the order of 0.3, which by convention is on the boundary between small and moderate effects. Some have interpretted these findings to mean that the clinical utility of antidepressant therapy has been overestimated and that the effects are not clinically significant for patients with milder forms of depressive illness. This presentation will summarize the findings of the meta-analytic studies that form the evidence base for this controversy and will examine the logic of the assumptions that underpin conclusions about the clinical significance of antidepressant effects. Results of several studies using novel statistical methods to assess the magnitude and clincial significance of antidepressant effects of RCTs will be presented. These findings will then be used to justify the conclusion that antidepressants have *large and clincially meaningful effects* for a significant minority of depressed participants in RCTs.

Learning Objectives:
- The participant will become familiar with the evidence underpinning the controversy about the magnitude of the effect of antidepressants
- The participant will learn about novel statistical methods to assess the clinical significance of treatment effects in RCTs

Literature References:
- Thase ME, Larsen KG, Kennedy SH. Assessing the 'true' effect of active antidepressant therapy v. placebo in major depressive disorder: use of a mixture model. Br J Psychiatry. 2011 Dec;199(6):501-7.
- Thase ME. The small specific effects of antidepressants in clinical trials: what do they mean to psychiatrists? Curr Psychiatry Rep. 2011 Dec;13(6):476-82.

WORKSHOP
2:00 PM – 5:00 PM
WORKSHOP OVERVIEW:
THE RIGHT ANSWER TO THE RIGHT QUESTION: MEETING THE GLOBAL CHALLENGES OF MEASUREMENT FOR EFFECTIVENESS STUDIES IN PSYCHIATRY

Mark G. Opler, Ph.D., MPH[1], Istvan Bitter[2], Toshiya Inada, M.D., Ph.D.[3], Anzalee Khan, Ph.D. [4], Madhukar Trivedi, MD[5]
[1]Department of Psychiatry, NYU School of Medicine, [2]Dept. Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary, [3]Institute of Neuropsychiatry, Seiwa Hospital, [4]ProPhase LLC; Nathan S. Kline Institute for Psychiatric Research, [5]UT Southwestern Medical Center

There is an increasing focus on evidence-based guidelines and effectiveness data to support clinical decision-making at the patient level and policy decisions at the institutional level (. Drug development researchers are being tasked with the design and execution of effectiveness (i.e. pragmatic) trials to demonstrate the utility of a new treatment in naturalistic settings, requiring a very different approach and understanding than efficacy trials (Hogarty, Schooler and Baker, 1997; Hoagwood, 1995). As the importance of effectiveness trials increases, the role of outcome measurement becomes critical to study success on several levels:

- Symptom severity is only one facet of effectiveness, and not necessarily a primary one at that – the field requires a renewed focus on innovation for endpoints such as functioning, quality of life, and similar outcomes that integrate different components of measurement in a more holistic fashion;
- Patient-reported outcomes as well as caregiver-reported outcomes require careful consideration as they may better meet the needs of effectiveness trials in some situations than clinician-rated outcomes that assess the similar constructs;
- Blinding and randomization may not be optimal and require investigators to consider carefully the impact these techniques may have on generalizability and consistency;
- The need for accurate demographic and contextual data is crucial to support appropriate statistical methods, particularly when randomization or blinding are not employed;
- Measure selection processes must take ecological validity and contextual relevance into greater account, and assumptions about measures being "gold-standard" for certain types of trials must be challenged.

In addition to general measurement principles, the impact of environment, country-specific, and regional differences are vital to trial success in patient-focused and "real-world" oriented studies. The metrics by which patients and clinicians define a treatment as "effective" are highly unlikely to be uniform (Kraemer et al 2011). Similarly, societal, community, and other group-level aspects can and should be considered.

In an effort to develop an integrated global outlook on effectiveness and the role of measurement, this workshop will include experts in measurement and psychometrics from Asia, Europe, and the United States. Each will discuss different challenges in measurement as they pertain to effectiveness trials, incorporating regional differences, individual and community perspectives, and related issues. The session will cover the roles of negative outcomes (i.e. adverse effects), language and culture, and new challenges in various clinical settings. Audience participation will be elicited through challenge questions and interactive, moderated question and answer sessions. By incorporating input from international participants, the workshop will attempt to conclude by summarizing the panel's recommendations and identifying the major challenges in global measurement for the coming era of effectiveness research

Learning Objectives:
- To review the challenges of measurement, data analysis, and interpretation in effectiveness (pragmatic) trials

- To explore and establish strategies for measurement selection, statistical approaches, and optimization for effectiveness trials

INDIVIDUAL ABSTRACT:
ARE REGIONAL DIFFERENCES IMPORTANT IN EFFECTIVENESS RESEARCH?
Istvan Bitter
Dept. Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

Treatment outcomes including effectiveness are measured by a few criteria worldwide. While center and country differences are routinely checked and reported there are very few studies specifically addressing it.

The Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) was a 3-year, prospective observational study including patients from 27 countries throughout Africa, Asia, Central and Eastern Europe (CEE), Latin America and the Middle. Monotherapy was prescriber at study entry for 5834 patients. Significant regional variations in the odds of remaining on the monotherapy prescribed at study entry were found with patients from Asia experiencing significantly lower odds of remaining on their original monotherapy, compared to patients from other regions. Further, patients in Latin America had significantly higher odds of remaining on monotherapy compared to patients in CEE (Latin America vs. CEE, OR: 1.4; 95% CI: 1.1–1.6; $p \leq .001$) (Bitter et al, 2007).

The World wide (W)-SOHO study was a 3-year, prospective, observational study that included 10 additional countries as compared to IC SOHO and over 17,000 outpatients with schizophrenia. This study confirmed earlier findings, that the course of schizophrenia seems to be more favorable in less developed countries. The authors found that approximately two-thirds of the patients (66.4%) achieved response during the 3-year follow up. Response rates varied across regions, and were highest in North Africa & Middle East (84.6%) and Latin America (78.6%) and lowest in Southern Europe (62.1%) and East Asia (60.9%). Their findings also indicate that response rates were higher in North Africa, in the Middle East and in Latin America than in Europe (Novick et al, 2012).

The use of observed case analysis in many naturalistic studies overestimates the treatment effects as compared to Last-Observation-Carried-Forward (LOCF) analysis.

Using employment or complex quality of life measures as outcome (effectiveness) criteria in multinational studies may obscure "real" treatment effects. For example the closure of big state owned factories in the former communist countries contributed to unemployment and homelessness (many factories provided accommodations for their employees). A 47-fold increase was registered in the unemployment rate in 1992 as compared to 1989, and there has been a significant increase in the number of disability pensions (Bitter, 2000).

Learning Objectives:
- understand the different outcome variables in schizophrenia studies
- To understand the possible effects of regional differences in treatment effects and clinical outcomes.

Literature References:
- Bitter, I et al: Antipsychotic prescription patterns in outpatient settings: 24-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. Eur Neuropsychopharmacol, 18(3): 170-180, 2008
- Novick,D et al: Regional differences in treatment response and three year course of schizophrenia

- Bitter, I: Mental disorders and economic change--the example of Hungary. Bull World Health Organ, 200; 78: 505-506, 2000

INDIVIDUAL ABSTRACT:
CLINICAL EVALUATION OF EXTRAPYRAMIDAL SYMPTOMS IN PSYCHIATRIC PATIENTS RECEIVING ANTIPSYCHOTICS USING THE DRUG-INDUCED EXTRAPYRAMIDAL SYMPTOMS SCALE (DIEPSS)
Toshiya Inada, M.D., Ph.D.
Institute of Neuropsychiatry, Seiwa Hospital

The rating scales for extrapyramidal symptoms (EPS) used in the clinical studies in the United States, such as Simpson and Angus Scale (SAS) and Extrapyramidal Symptoms Rating Scale (ESRS) by Chouinard et al (1980), were very old and were developed in the era of first-generation antipsychotics. The prevalence of EPS has decreased since the introduction of second-generation antipsychotics. However, some patients still have a high EPS risk and often develop severe EPS during the treatment with these drugs. Therefore, to evaluate EPS in the clinical practice is still an important requirement that mustn't be lost for all psychiatrists. Given the now relatively low incidence of EPS in psychiatric patients receiving second-generation antipsychotic drugs, EPS scales with many items, such as the ESRS or the combined use of SAS and other rating scales, may be considered too burdensome for general clinical use.
Unlike the SAS or the ESRS, which are so-called first-generation EPS scales designed to record the high level of EPS seen with first-generation antipsychotics, the drug-induced extrapyramidal symptoms scale (DIEPSS) is a very simple design consisting of 8 individual items and 1 global item. Regardless of its simplicity, DIEPSS has a profile of high sensitivity and reliability, that is appropriately matched to the EPS profiles of current antipsychotic drugs. It is actually called a second-generation EPS scale; its simplicity and high reliability make it suitable for assessing the low incidence of EPS in the era of second-generation antipsychotics. It has become a standard rating scale for the evaluation of EPS in Japan, especially in clinical trials of atypical antipsychotic drugs. The DIEPSS is also recommended as a screening instrument in the outpatient clinic to allow the detection of early manifestations of EPS, because the items included encompass the whole range of EPS, from acute signs seen in the early stages of treatment to tardive dyskinesia.
In view of simplicity and practical usefulness of DIEPSS, it is expected to gradually replace first-generation EPS evaluation methods such as the ESRS, or combined use of the SAS and other rating scales. The DIEPSS has an excellent training system that includes videoclips showing various severities of all individual items. In the present session, clinical profiles of DIEPSS are introduced showing several representative videoclips to grasp the excellent profiles of this second generation rating scale.

Learning Objectives:
- How to evaluate the severity of antipsychotic-induced extrapyramidal symptoms in the era of second generation antipsychotics.
- To learn the simplicity and excellent sensitivity and reliability of drug-induced extrapyramidal symptoms scales (DIEPSS)

Literature References:
- Inada T: DIEPSS: A second-generation rating scale for antipsychotic-induced extrapyramidal symptoms: Drug-induced Extrapyramidal Symptoms Scale. Seiwa Shoten Publishers, Inc, Tokyo, September 17, Text pp1-49 & Appendix pp1-21, 2009.

- Inada T, Beasley C, Tanaka Y, Walker D: Extrapyramidal symptom profiles assessed with DIEPSS: comparison with western scales in the clinical double-blind studies of schizophrenic patients treated with either olanzapine or haloperidol. Int Clin Psychopharmacol 18: 39-48, 2003.

INDIVIDUAL ABSTRACT:
STATISTICAL APPROACHES IN EFFECTIVENESS TRIALS
Anzalee Khan, Ph.D., Psychometrics
ProPhase LLC; Nathan S. Kline Institute for Psychiatric Research
The goal of most trials, effectiveness or efficacy, is to show that the treatment under review would be an improvement on current clinical practice. Although effectiveness studies are closer to what is seen and done clinically, appropriate analysis is essential to show the real potential of the treatment. In order to adapt the study protocol to routine daily practice, a multistep analysis needs to be designed as not all patients are in the same treatment step at the same time, and the period of time between finishing the treatment and registration of the primary outcome may vary across patients. While designing trials to better meet decision makers' needs is appealing, effectiveness trials raise unique analytical issues and are essential to all aspects of the trial from beginning to end. For example, 45 years ago, statisticians, Schwartz and Lellouch (1967) described the appropriate selection of outcomes to be evaluated in effectiveness trials and described how closely linked the analytic decisions are to the selection of individuals for inclusion in trials. Additionally, a larger sample is needed for effectiveness trials as the researcher is recruiting from a wider population with a more heterogeneous mix of patients. Therefore, the variability between patients dilutes the treatment effect but does not undermine the credibility of an effectiveness trial. Unlike efficacy trials, statistical analysis in effectiveness trials must be a major part of study design and all subsequent phases of the trial as everyone is evaluated on an Intent-to-treat basis. Some statistical methods include: imputation techniques for missing data, tools to explore differences between enrolled trial patients before the start of treatment, and Bayesian analytic approaches may be useful for effectiveness trials. An important feature of Bayesian approaches is that they allow estimation of subgroup treatment effects by combining the observed subgroup effect and the overall treatment effect using weights that reflect the a priori view of the degree and direction of heterogeneity.
Use of effectiveness trials, requires careful consideration of important analytic approaches. There are statistical approaches to mitigate the bias introduced by the imbalances that can be obtained in effectiveness trials and standard inferential procedures are likely to lead to invalid conclusions. With the growing awareness of the importance of data from effectiveness trials for health care decision-making, considerable progress has been made in establishing guidance for design and analysis of effectiveness trials.
In this presentation, the major statistical issues that arise in the analysis of data from effectiveness trials, with particular reference to the limitations of existing approaches, and recent methodological developments will be reviewed. Adjustment techniques, stratification methods, instrumental variable and bayesian procedures will be reviewed. The emphasis will be on nontechnical aspects of the procedures.
Learning Objectives:
- This course is designed to teach clinicians and new researchers how to incorporate appropriate statistical techniques for effectiveness trials. Participants will also be presented with models and techniques for analyzing effectiveness trials.

- Participants will learn the contrasts of explanatory with effectiveness trials, point to the differences in the ways in which trial data are analyzed and interpreted, and discusses the power of replication, a defining feature of the scientific method.

Literature References:
- van der Windt DA, Koes BW, van Aarst M, Heemskerk MA, Bouter LM: Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. Br J Gen Pract 2000, 50(454):371-4.
- Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, Lam M, Seguin R: Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol 2003, 3:28

INDIVIDUAL ABSTRACT:
MEASUREMENT OF OUTCOMES FOR DEPRESSION: A US INVESTIGATOR'S PERSPECTIVE
Madhukar Trivedi, M.D.
UT Southwestern Medical Center

Remission has been widely accepted as the desired outcome for Depression. Although a significant attention has been paid to the reduction in symptoms based on DSM-IV criteria utilizing specific symptom rating scales, remission even from the outset has been defined as return to premorbid function. This must therefore entail more than mere reduction in symptoms. Furthermore, some of the most commonly reported residual symptoms are seen in associated domains like cognition, social functioning, motivation, etc. These residual symptoms are often associated with continuing poor performance in work and social domains and are also harbingers of relapse and recurrence.

The large NIMH-funded clinical trials like STAR*D, COMED, REVAMP, and STEP-BD demonstrated the potential power of Measurement Based Care guided by an algorithm in the management of mood disorders. However, they also highlighted the limitations of simple measurements based on symptoms defined narrowly through DSM-IV criteria. These and other large scale studies in the US have also revealed the importance of other critical outcomes not addressed through these measurements, including treatment adherence, persistence in treatment, and social and work functioning. In addition other disease aspects like medical comorbidity and environmental factors can also have significant impact on the patient's ability to achieve remission and return to premorbid functioning.

Furthermore, another aspect seldom addressed but playing an important role in adherence and persistence is likely to be the individual's goals of treatment that are often not purely defined in terms of symptoms but focus on broader concepts. More importantly, little attention has been paid to the assessments of outcomes based on specific targets/mechanisms of the antidepressant being evaluated. Finally, measurements used in traditional clinical trials have failed to capture important aspects of the disease modifying processes that can be understood based on advances in clinical neuroscience.

Lessons learned from our work through these large clinical trials in depression will be discussed and novel approaches will be presented that address concerns raised above.

Learning Objectives:
- Discuss approaches to measurement of outcomes.
- Discuss goals of treatment outcomes beyond symptoms in depression.

Literature References:

- Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L, Norquist, G., Howland, R.H., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M. Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. The American Journal of Psychiatry, 2006;163(1):28-40.
- Trivedi, M.H., Fava, M., Wisniewski, S.R., Thase, M.E., Quitkin, F., Warden, D., Ritz, L., Nierenberg, A.A., Lebowitz, B.D., Biggs, M.M., Luther, J. F., Shores-Wilson, K., Rush, A.J. Medication Augmentation after the Failure of SSRIs for Depression. New England Journal of Medicine, 2006;354(16):1243-52.

Friday, May 31, 2013

PANEL
8:30 AM – 10:00 AM
PANEL OVERVIEW:
NEW THERAPEUTIC OPPORTUNITIES FOR THE TREATMENT OF DEPRESSION

Maurizio Fava, M.D.[1], Marianne Dragheim, M.D.[2], Ronald M. Burch, M.D., Ph.D.[3], Emiliangelo Ratti, M.D.[4], Jonathan E. Alpert, M.D.,Ph.D.[5]
[1]Massachusetts General Hospital, [2]H. Lundbeck A/S, [3]Naurex, Inc., [4]NeRRe Therapeutics Ltd, [5]Massachusetts General Hospital, Harvard Medical School

There are clear limitations to the currently approved pharmacotherapies of depression, including the fact that they have modest efficacy and a relatively slow onset of efficacy, and suffer from significant tolerability issues, particularly in the long term, including sexual dysfunction, weight gain, and cognitive impairments. This panel will review some of the most promising novel mechanisms that are not represented in compounds currently approved for depression in either the United States or Europe and that may represent the future of the psychopharmacologic treatment of depression, potentially addressing some of the efficacy and tolerability issues of antidepressants on the market. These potential antidepressant treatments include the multimodal serotonergic agents, the triple uptake inhibitors, the neurokinin-based novel therapies, and the glutamatergic treatments. Some of these mechanisms appear to be more advanced in terms of drug development than others, but they all contribute to the global effort to develop more effective and better tolerated treatments for major depressive disorder. Dr. Tran will present the pharmacology and the clinical evidence for the antidepressant efficacy of amitifadine, a triple reuptake inhibitor with the greatest potency towards serotonin reuptake (5-HT), half as much towards norepinephrine reuptake (NE) and one eighth towards dopamine reuptake (DA). Dr. Dragheim will review the pharmacological mechanisms and the results from several short-term placebo controlled studies of vortioxetine, an antidepressant with multimodal activity that combines receptor activity modulation and serotonergic reuptake inhibition. Dr. Ratti will review the rationale for the development of the hypothesis that the full and long lasting blockade of the NK1 receptors may be a critical requirement for the antidepressant effects of NK1 antagonists and will present the clinical efficacy data concerning casopitant and orvepitant, two NK1 receptor antagonists. Finally, Dr. Burch will present the evidence in support of the antidepressant efficacy of Naurex's lead compound, GLYX-13, a novel and selective NMDAR partial agonist in development as an adjunctive therapy for patients with depression.
Learning Objectives:

- To become familiar with the pharmacological actions and the evidence of antidepressant efficacy of novel compounds under development for the treatment of depression.
- To understand how new molecular targets may provide novel therapeutic approaches to the treatment of depression.

INDIVIDUAL ABSTRACT:
EFFICACY AND SAFETY OF VORTIOXETINE, AN NOVEL MULTIMODAL ANTIDEPRESSANT
Marianne Dragheim, M.D.
H. Lundbeck A/S

There are clear limitations to the currently approved antidepressants, including modest efficacy, persisting residual symptoms and tolerability issues, particularly in the long term, including sexual dysfunction, weight gain, and cognitive impairments. A novel compound such as vortioxetine (Lu AA21004) with its unique properties might address some of the current clinical unmet needs.

This presentation will review the pharmacological mechanisms of vortioxetine and the efficacy and safety results from several studies. Vortioxetine is currently under evaluation by several authorities including the FDA. It is a multimodal antidepressant and is thought to work through a combination of two pharmacological modes of action: modulation of receptor activity and transporter inhibition. In vitro studies indicate that vortioxetine is a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the serotonin transporter. In vivo non-clinical studies have demonstrated that vortioxetine enhances levels of the neurotransmitters serotonin, noradrenaline, dopamine, acetylcholine and histamine in specific areas of the brain. The novel mechanism of action of vortioxetine may provide benefit to the patient in terms of an effective pharmacological treatment with additional advantages including an improved tolerability relative to other antidepressants.

The vortioxetine global clinical development program included more than 7,500 individuals exposed to the compound. It has been investigated in several short-term placebo controlled studies, including one dedicated study in the elderly. The studies have been conducted in regions throughout the world and support robust and statistically significant efficacy of vortioxetine in a dose range of 5 to 20 mg per day. Efficacy of vortioxetine was also demonstrated in a long-term relapse-prevention study in major depression. Vortioxetine is well tolerated in adults and the elderly, with nausea being the only adverse event with an incidence ≥10% and higher than placebo. The safety profile of vortioxetine is favorable relative to other antidepressants with insomnia, somnolence, weight, vital signs, ECGs (including QTc), and clinical safety laboratory tests at placebo level, and with respect to sexual dysfunction and discontinuation symptoms.

Learning Objectives:
- To become familiar with the pharmacological modes of action of vortioxetine.
- To become familiar with the evidence of efficacy and safety of vortioxetine.

Literature References:
- Mørk A, Pehrson A, Brennum LT, Nielsen SM, Zhong H, Lassen AB, Miller S, Westrich L, Boyle NJ, Sanchez C, Fischer CW, Liebenberg N, Wegener G, Bundgaard C, Hogg S, Bang-Andersen B, Stensbol TB. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. J Pharmacol Exp Ther 2012;340:666-675.

- Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active-reference study of Lu AA21004 in patients with major depressive disorder (MDD). Int J Neuropsychopharmacol 2012;15:589-600.

INDIVIDUAL ABSTRACT:
NK-1 ANTAGONISTS: A POTENTIAL NOVEL CLASS OF ANTIDEPRESSANT AGENTS
Emiliangelo Ratti, M.D.
NeRRe Therapeutics, Ltd

All currently approved pharmacologic treatments for Major Depressive Disorder (MDD) are based on monoaminergic mechanisms. The large number of patients who neither respond to nor tolerate current therapies has led to exploration of novel mechanisms in the belief that these will lead to improvements in onset of action, spectrum of efficacy and/or tolerability. One such mechanism is the antagonism of substance P (SP, the endogenous NK1 receptor ligand) through the blockade of the neurokinin-1 (NK1) receptors.

Numerous studies have demonstrated that SP and NK1 receptors are located in areas of the brain involved in the regulation of affect and stress behaviors, including the amygdala, hypothalamus, hippocampus, frontal cortex, raphe nucleus, and locus coeruleus. There is also considerable overlap between the SP-NK1 receptor system and neurotransmitters known to be involved in depression (e.g. serotonin, noradrenaline) in terms of co-localization and functional interaction. Central injections of NK1 receptor agonists induce distress in animal models, whereas administration of NK1 receptor antagonists reduce distress, suggesting anxiolytic properties. In addition cerebrospinal fluid taken from depressed or anxious patients has shown increased levels of SP compared to normal controls.

The hypothesis that NK1 receptor antagonists may be effective antidepressants is supported by clinical data in patients with major depressive disorder (MDD) using different selective NK1 antagonists. In an initial study, aprepitant (MK-869) 300mg/day (estimated to provide ≥95% NK1 central receptor occupancy [RO] in the human brain) achieved clinically meaningful separation from placebo. This was followed by trials with two other NK1 antagonists; L-759274 and an unpublished study with CP122721 with both reporting positive efficacy findings. Five further studies with aprepitant, using a revised nano-milled formulation, with doses up to 160 mg/day (estimated to provide ~92% RO) failed to demonstrate efficacy, including two studies in which the positive control, paroxetine, separated from placebo. However, recent clinical studies performed with new generation of NK1 antagonists, casopitant and orvepitant, with physicochemical characteristics able to provide full and long lasting saturation of the central NK1 receptor compartment, showed that a significant antidepressant effect could be achieved. These data have led to the development of the hypothesis that the full and long lasting blockade of the NK1 receptors may be a critical requirement for the antidepressant effects of NK1 antagonists.

The casopitant and orvepitant NK1 receptor occupancy data together with the clinical data obtained in four clinical studies in depressed patients performed with these two molecules will be presented and discussed.

The data taken together suggest that NK1 antagonists, able to provide full and long lasting saturation of the central NK1 receptor compartment could deliver a novel generation of differentiated antidepressant agents.

Learning Objectives:

- To become familiar with the evidence in support of the antidepressant properties of NK1 antagonists
- How Nk1 antagonists can deliver a differentiated antidepressant profile

Literature References:
- Kramer MS et al: Demonstration of the Efficacy and Safety of a Novel Substance P (NK1) Receptor Antagonist in Major Depression. Neuropsychopharmacology (2004) 29, 385–392
- Ratti E et al: Results from 2 randomized, double-blind, placebo-controlled studies of the novel NK1 receptor antagonist casopitant in patients with major depressive disorder. J Clin Psychopharmacol. 2011 Dec;31(6):727-33

INDIVIDUAL ABSTRACT:
OPIOID MODULATION: A NOVEL MECHANISM FOR THE TREATMENT OF DEPRESSION: RESULTS OF THE ALKS 5461 PHASE 2 STUDY
Maurizio Fava, M.D.
Massachusetts General Hospital

Background: The endogenous opioid system is thought to play a key role in the regulation of mood. The contemporary use of opioids for depression is limited by abuse potential, presumably a result of mu opioid agonism. ALKS 5461 is a co-formulation of buprenorphine (BUP), a partial mu agonist, combined with ALKS 33, a counter-acting mu antagonist designed to yield a non-addictive opioid modulator. ALKS 33 component was optimized to be highly potent and sublingually bioavailable with the latter two properties being essential for sublingual co-formulation. A phase II study was conducted to confirm preliminary evidence of anti-depressive efficacy observed in an earlier phase I/II pilot study of ALKS 5461.
Methods: 142 patients with major depressive disorder (MDD) and inadequate response to SSRI or SNRI therapy in the current depressive episode were enrolled. A blinded sequential parallel comparison design (SPCD) with two 4-week treatment stages was utilized, and the data from all subjects in phase 1 were pooled with the data from the placebo non-responders rerandomized to treatment with active therapy or placebo in phase 2. Treatment groups included 2 mg/2 mg BUP/ALKS 33, 8 mg/8 mg BUP/ALKS 33, and matching placebo. All subjects, including those assigned to placebo treatment, remained on background SSRI/SNRI therapy.
Results: Results from the study showed that ALKS 5461 significantly reduced depressive symptoms across a range of standard measures, including the study's primary outcome measure, the 17-Item Hamilton Depression Rating Scale (p=0.026), as well as secondary measures including the Montgomery-Åsberg Depression Rating Scale (p=0.004) and the Clinical Global Impression – Severity Scale (p=0.035). The most common AEs observed in the study included nausea, vomiting and sedation, typical of opioid therapy.
Conclusions: ALKS 5461 demonstrated significant and clinically meaningful improvement in depressive symptoms among patients with an inadequate response to SSRI/SNRI therapy. Combined with the findings from the prior pilot study, these results indicate that opioid modulation may be a novel and important new treatment approach for this serious and chronic disease.

Learning Objectives:
- Understand the therapeutic potential of opioid modulation for major depressive disorder.
- Understand the treatment implications of ALKS 5461 from study results on several efficacy assessments.

Literature References:
- Bodkin JA, et al. Buprenorphine treatment of refractory depression. J Clin Psychopharmacol 1995; 15:49-57
- Fava M., Evins A., Dorer D., Schoenfeld D.: The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach; Psychotherapy and Psychosomatics 2003; 72:115-127; and "Erratum" 2004; 73: 123.

INDIVIDUAL ABSTRACT:
RAPID ANTIDEPRESSANT EFFECT OF GLYX-13, A NOVEL AND SELECTIVE NMDAR PARTIAL AGONIST

Ronald M. Burch, M.D., Ph.D.
Naurex, Inc

NMDA receptor ligands have been shown to rapidly treat depression but are associated with psychotomimetic effects. GLYX-13 is an NMDA receptor (NMDAR) glycine site functional partial agonist with ~ 25% of the agonist activity of glycine or D-serine. Animal models suggest a single intravenous dose may produce long-term efficacy without psychotomimetic effects.

Objective: A single intravenous dose,phase II randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of GLYX-13 with central raters in subjects who had failed at least one antidepressant during the current episode.

Methods: Subjects had failed (<25% response) at least one adequate therapeutic trial with an antidepressant during the current episode assessed using the ATRQ. All antidepressant agents were discontinued prior to the GLYX-13 dose and for the subsequent 14 or 28 day observation period following the single dose. Subjects, 48 male and 68 females, received a single intravenous dose of GLYX-13 (1,5, 10, or30mg/kg) or placebo. Central raters assessed subjects via telephone using the HDRS-17 at Screening, Baseline, Days 1, 3, 7, 14, 21 and 28, the Bech-6 at 2, 4, 8, and 12 hours, andBPRS+ to assess behavioral side effects at 45, 60 and 90 minutes, and 2, 4, 6, 12 and 24 hours.

Results: MMRM revealed reduction in HDRS-17 total score versus placebo at Days 1, 3,and 7, with return to placebo level at Day 7. GLYX-13 was associated with no specific adverse events and did not cause psychotomimetic side effects at any dose studied.

Conclusion: This study finds that a single intravenous dose of GLYX-13, an NMDA receptor glycine site functional partial agonist, rapidly reduces depression scores without eliciting psychotomimetic effects at therapeutic doses as assessed by central raters. . A repeated dose trial of adjunctive GLYX-13 in subjects with inadequate response to antidepressant therapy is ongoing. The results of this study suggest that NMDAR modulators may provide rapid efficacy in patients with depression inadequately treated using SSRI/SNRI antidepressants without causing the dissociative/psychotomimetic side effects observed following treatment with full NMDAR antagonists.

Learning Objectives:
- To become aware of the mechanisms underlying efficacy and side effects of NMDA glycine site modulators
- To become aware of the mechanisms underlying efficacy and side effects of NMDA glycine site modulators

Literature References:

- Moskal JR, Kuo AG et al. GLYX-13, a monoclonal antibody-derived peptide that acts as an N-methyl-D-aspartate receptor modulator. Neuropharmacology. 2005; 49:1077-1087.
- Zarate CA, Singh JB etal. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant depression. 2006; 63: 856-864.

GENERAL DISCUSSION
Jonathan E. Alpert, M.D., Ph.D.
Massachusetts General Hospital, Harvard Medical School

PANEL
8:30 AM – 10:00 AM
PANEL OVERVIEW:
PURSUING UNMET NEEDS IN THE TREATMENT OF COCAINE AND MARIJUANA ADDICTION: NEW CLINICAL TRIALS OF POTENTIALLY BREAKTHROUGH THERAPIES IN NIDAS CLINICAL TRIALS NETWORK

Steven Sparenborg, Ph.D.[1], Theresa Winhusen, Ph.D.[2], Christie Thomas, MPH[3], Kevin M. Gray, M.D.[4], Madhukar Trivedi, M.D.[5]
[1]Center for the Clinical Trials Network, NIDA, NIH, [2]University of Cincinnati College of Medicine, [3]UCLA, [4]Medical University of South Carolina, [5]UT Southwestern Medical Center

Dr. Sparenborg will briefly present recent and ongoing development in The National Drug Abuse Treatment Clinical Trials Network (CTN). The CTN was created by the National Institute on Drug Abuse in 1999. Its purpose is to conduct clinical trials that will form the foundation of evidence-based treatments useful to practitioners. The CTN consists of 18 principal investigators and nearly 200 treatment sites affiliated with more than 50 universities and VA hospital centers. Eleven trials of FDA-approved medications have been conducted in the CTN, enrolling more than 4000 patients.

With the advent of the Parity Act and the Affordable Care Act, the CTN is turning its eye toward the unmet need of integrating addiction care into mainstream medical services, including primary and emergency care, to reach a larger number of patients who might not otherwise seek treatment for addictions. Effective fulfillment of this unmet need could be facilitated by medication-related evidence developed in the CTN as well as the development of effective SBIRT practices and widespread use of electronic medical records using common data elements useful to all levels of medical care.

High rates of cigarette smoking co-morbidity in stimulant abusers led Dr. Winhusen to explore the feasibility of treating such co-morbid patients for both dependencies. In the most recently completed trial in the network, cigarette-smoking stimulant abusers seeking treatment for cocaine/methamphetamine dependence were offered smoking cessation treatment and the effects of the simultaneous treatments on stimulant use, other drug/alcohol use, and smoking outcomes were measured. The findings from the trial and implications for how best to address the co-occurring problems of nicotine dependence and cocaine/methamphetamine-dependence will be discussed.

Dr. Winhusen is leading a CTN study of buspirone as a treatment for cocaine relapse prevention. Dramatic pre-clinical demonstrations of the influence of D3 and D4 antagonists on cocaine use reductions and the discovery that buspirone has potent D3/D4 receptor activity suggest that drugs such as buspirone could be breakthrough therapies in the unmet need for stimulant abuse treatment.

Drs. Ling and Mooney investigate the use of buprenorphine (BUP) for cocaine dependence treatment. Trials of BUP have shown substantial reductions in cocaine usage among opiate users. This CTN study examines the utility of BUP, in the presence of mu receptor blockade with sustained-released naltrexone, in reducing cocaine use in cocaine-dependent patients with minimal experience with opiates.

Dr. Gray explores the use of N-acetylcysteine (NAC) as a treatment for marijuana addiction. Based on encouraging preclinical research demonstrating NAC's effects on addiction-induced glutamate dysfunction, Dr. Gray's team conducted an initial randomized trial of NAC targeting marijuana addiction in adolescents, demonstrating NAC's efficacy in this population. In order to evaluate NAC's potential role in treatment across a broader age spectrum, this new CTN placebo-controlled randomized trial will test its effects in marijuana-addicted adults.

Learning Objectives:
- Improve understanding of the organizational structure, past accomplishments, and the new directions of the CTN.
- Learn results of the new study of bupropion and nicotine for smoking cessation offered simultaneously with treatment as usual for stimulant dependence.
- Understand the pharmacological rationales of potential breakthrough therapies of buspirone, buprenorphine, and n-acetyl cysteine for cocaine and marijuana addictions.

INDIVIDUAL ABSTRACT:
N-ACETYLCYSTEINE FOR MARIJUANA ADDICTION: RATIONALE AND DESIGN FOR A PLACEBO-CONTROLLED RANDOMIZED TRIAL IN NIDAS CLINICAL TRIALS NETWORK

Kevin M. Gray, M.D.
Medical University of South Carolinaf

Marijuana addiction is an increasingly prevalent and significantly under-addressed condition. Preclinical research has demonstrated the important role of the neurotransmitter glutamate in addictive processes. By re-equilibrating glutamate levels via activation of the cystine-glutamate exchanger in the nucleus accumbens, NAC directly normalizes drug-induced pathology and exerts significant behavioral effects in animal models of addiction. Based on these findings, and the appeal of NAC as a well-tolerated and widely available over-the-counter supplement, Dr. Gray's team conducted an initial placebo-controlled randomized trial of NAC in marijuana-addicted adolescents. This trial demonstrated NAC's efficacy as an adjunct to psychosocial treatment in youth. In order to evaluate NAC's potential role in treatment across a broader age spectrum, this new placebo-controlled randomized trial will test its effects in marijuana-addicted adults. The NIDA Clinical Trials Network provides the ideal platform to efficiently carry out this large-scale study. Dr. Gray will discuss the design of this upcoming trial and its role in addressing a significant public health need.

Learning Objectives:
- Learn about evidence supporting N-acetylcysteine as a glutamate-targeted addiction pharmacotherapy.
- Understand the rationale supporting the design of the upcoming NIDA Clinical Trials Network trial of N-acetylcysteine as a treatment for marijuana addiction.

INDIVIDUAL ABSTRACT:

NIDA CTN PHARMACOLOGICAL TRIALS FOR STIMULANT-DEPENDENCE: RECENT FINDINGS AND CURRENT TARGETS

Theresa Winhusen, Ph.D.
University of Cincinnati College of Medicine

Cocaine- and methamphetamine-dependence represent important public health problems for which there are currently no FDA-approved pharmacological treatments. This presentation will discuss clinical trials using two different approaches for treating stimulant dependence. One approach is to target stimulant dependence directly. The NIDA Clinical Trials Network (CTN) is currently conducting a clinical trial to test buspirone, a dopamine D3 and D4 antagonist, as a relapse prevention treatment in cocaine-dependent patients in inpatient/residential treatment scheduled for outpatient treatment post-discharge. Pre-clinical data providing a rationale for evaluating buspirone as a cocaine relapse-prevention treatment will be discussed. A second approach to treating stimulant dependence is to target co-occurring conditions that may make abstinence from cocaine/methamphetamine more difficult to maintain. Cigarette smoking is prevalent in cocaine/methamphetamine-dependent patients and is associated with significant morbidity and mortality. The NIDA CTN conducted a 10-week, two-group, randomized trial to evaluate the impact of providing smoking cessation treatment (SCT) with SUD treatment as usual (TAU), compared to TAU alone, on stimulant-use outcomes in smokers who were in outpatient treatment for cocaine or methamphetamine dependence. The trial was specifically designed to evaluate the relationship between cigarette smoking and illicit stimulant use, which prior research suggests is linked. The study included a total of 538 participants who smoked at least 7 cigarettes per day and wished to stop smoking and who met DSM-IV-TR criteria for cocaine and/or methamphetamine dependence. The findings from this trial and implications for how best to address the co-occurring problems of nicotine dependence and cocaine/methamphetamine-dependence will be discussed.

Learning Objectives:
- To learn about the impact that concurrently providing smoking cessation and substance-abuse treatment had on substance use outcomes in a sample of cocaine- and/or methamphetamine-dependent cigarette smokers.
- To better understand the rationale for evaluating buspirone for relapse-prevention in cocaine dependence.

Literature References:
- Winhusen T, Brady KT, Stitzer M, Woody G, Lindblad R, Kropp F, Brigham G, Liu D, Sparenborg S, Sharma G, VanVeldhuisen P, Adinoff B, Somoza E, Evaluation of buspirone for relapse-prevention in adults with cocaine dependence: An efficacy trial conducted in the real world, Contemporary Clinical Trials. 2012; 33: 993-1002.
- Winhusen T, Stitzer M, Woody G, Brigham G, Kropp F, Ghitza U, Lindblad R, Adinoff B, Green C, Sharma G, Somoza E. Design considerations for a study to evaluate the impact of smoking cessation treatment on stimulant use outcomes in stimulant-dependent individuals. Contemporary Clinical Trials. 2012; 33 (1): 197-205.

INDIVIDUAL ABSTRACT:
COCAINE USE REDUCTION WITH BUPRENORPHINE (CURB) STUDY

Christie Thomas, M.P.H.

Concerted effort over three decedes has not produced an effective and safe medication for cocaine dependence although several promising candidates have emerged among them the partial

mu opioid agonist buprenorphine, widely prescribed for the treatment of opioid dependence and shown in animal studies to block stress induced reinstatement of cocaine self administration, the latter attributed to its kappa antagonism. Clinical studies in opioid addiction have suggested that buprenorphine may reduce cocaine use in humans. However, concerns over inducing opioid dependence have prevented systematic testing of buprenorphine in cocaine pharmacotherapy until recently when clinical and laboratory evidence showed that the buprenorphine mu effect can be blocked by co-administration of naltrexone, allowing its kappa antagonism and other non-mu effects to be tested independently. This NIDA CTN multi-site trial examined the effects of buprenorphine on cocaine use, compared to placebo, in 302 cocaine dependent individuals with minimal history of opioid exposure, under the condition of mu blockade by co-administration of sustained-released naltrexone. After induction onto sustained-release naltrexone, participant were randomly assigned in equal numbers to placebo daily, buprenorphine 4 mg daily, or buprenorphine 16 mg daily, for 8 weeks, with a second naltrexone injection administered after week 4. Participants provided urine toxicology specimens 3 times weekly and reported on their cocaine use for every day of the 8 week period. Number of cocaine-free days during the final 30 days of the study will be compared across study conditions and used as the primary treatment outcome. The study has completed its subject enrollment at the end of October, 2012, 9 months ahead of schedule.

Learning Objectives:
- The NIDA Clinical Trial Network's contribution to clinical treatment research
- Medication combinations as a novel strategy in medical development

Literature References:
- Gerra G, Fantoma A, and Zaimovic A. (2006) "Naltrexone and buprenorphine combination in the treatment of opioid dependence." Journal of Psychopharmacology; 20(6): 806-14.
- George Koob (2012) "A combination of buprenorphine and naltrexone blocks compulsive cocaine intake in rodents without producing dependence." Science Translational Medicine. August, 2012

GENERAL DISCUSSION
Madhukar Trivedi, M.D.
UT Southwestern Medical Center

PANEL
8:30 AM – 10:00 AM
PANEL OVERVIEW:
REDISCOVERING CATATONIA: THE IMPACT OF NEW DSM-5 CLASSIFICATION
Georgios Petrides, M.D.[1], Stanley N. Caroff, M.D.[2], Dirk Dhossche[3], Gregory Fricchione[4], Max Fink, M.D.[5]
[1]The Zucker Hillside Hospital, Northshore-LIJ Health System, [2]Philadelphia VA Medical Center and the Perelman School of Medicine, University of Pennsylvania, [3]University of Mississippi Medical Center, [4]Massachusetts General Hospital, [5]Stony Brook University School of Medicine
There is renewed interest in the syndrome of catatonia as in the forthcoming DSM-5 "catatonic schizophrenia" (295.2) will be deleted and a new independent class of "catatonia not elsewhere classified" (299.98) will be added. This is recognition that catatonia, the same way as psychosis or cognitive impairment, can be seen in multiple psychiatric and medical conditions independent

of schizophrenia. This new classification, which is in line with NIMH's RDoC, offers new opportunities to study the biological underpinnings of this condition offering more homogeneous populations for clinical trials, neuroimaging and genetic studies. This symposium aims at discussing these areas of interest in catatonia recognition, treatment, and research.

Catatonia is inferred by the presence of two or more motor symptoms (mutism, negativism, posturing, repetitive behaviors, echopraxia, autonomic instability and many others) for 24 hours. The presence is verified by the positive immediate relief by an intravenous injection of a barbiturate (amobarbital) or benzodiazepine (the "lorazepam relief test"). The syndrome is effectively treated by high doses of benzodiazepines or barbiturates, or when this fails, by ECT. Prompt recognition and treatment is essential as medical complications may be life-threatening in some cases.

Surveys using catatonia rating scales find catatonia in about 10% of hospitalized psychiatric patients. Catatonic symptoms are identified in many conditions including affective disorders, schizophrenia, neuroleptic malignant syndrome, epilepsy, CNS infections, injuries and ischemia, and at times without an identifiable underlying disorder. A population of interest is children and adolescents where increased prevalence has been reported in first-break psychosis, autistic patients with intractable tics, aggression or self-injury, and pediatric patients diagnosed with the newly coined anti-NMDAR encephalitis.

Recognition of catatonia in vulnerable populations, the various types of catatonic presentation will be discussed. Emphasis will also be given on the treatment of catatonia, it's the underlying biology and implications for new drug development.

Overall this symposium will highlight the renewed interest in the catatonic syndrome that will now be dissociated from schizophrenia in DSM-5 and the new opportunities for integrated research in more homogeneous populations.

 Learning Objectives:
- The audience will be familiar with the new classification of catatonia in DSM-5.
- The audience will be familiar with new research prospectives in the field of catatonia.

INDIVIDUAL ABSTRACT:
REDISCOVERING CATATONIA: THE IMPACT OF NEW DSM-5 CLASSIFICATION
Max Fink, M.D.
Stony Brook University School of Medicine
Objective: Catatonia, a disorder of movement and mood, was described and named in 1874. Other observers quickly made the same recognition.

By the turn of the century, however, catatonia was incorporated as a type within a conjured syndrome of schizophrenia. There, catatonia has lain in the psychiatric classification for more than a century.

Methods: We review the history of catatonia and its historical status in the DSM classifications I-IV. The DSM-5 proposes radical changes deleting schizophrenia, catatonic type (295.2) and inserting a new class, Catatonia Not Elsewhere Classified (298.99).

Results: The new classification encourages the recognition of many forms of catatonia including NMS, delirious mania, anti-NMDAR encephalitis, Tourette syndrome, and catatonia in autism spectrum disorders. The new classification will encourage better recognition and effective treatment as catatonia is eminently treatable.

Conclusions: The recommended changes in the catatonia classification will direct attention to new treatments related to the activity of benzodiazepines and increased attention to the mechanisms of ECT.

Learning Objectives:
- Impact of these changes on clinical diagnosis and treatment in schizophrenia.

Literature References:
- Fink, M. Rediscovering Catatonia: The Biography of a Treatable Syndrome, Acta psychiatr scand 2013; Supplement 441:127: 1-47
- See APA website for update on DSM-5:www.dsm5.org/Proposed revision/Pages/SchizophreniaSpectrumandotherpsychotic disorders/aspx

INDIVIDUAL ABSTRACT:
UPDATE ON PEDIATRIC CATATONIA
Dirk Dhossche
University of Mississippi Medical Center
There has been renewed interest in the demarcation of the catatonic syndrome from other pediatric conditions including autism, yielding new information on prevalence, symptoms, treatment, risk factors, and experimental models of pediatric catatonia. Recent prevalence rates of pediatric catatonia vary widely across studies, but are elevated in adolescents with first-break psychosis, autistic patients with intractable tics, aggression or self-injury, and pediatric patients diagnosed with the newly coined anti-NMDAR encephalitis. These observations support that catatonia is more prevalent in children and adolescents than previously thought. Current experience shows that symptoms, diagnostic criteria, and treatment options (benzodiazepines and electroconvulsive treatment) for pediatric catatonia are the same as in adults but systematic studies are lacking. Sometimes catatonia is precipitated by severe stress and trauma. Historical and contemporary clinical and experimental catatonia models focusing on motor circuitry dysfunction, abnormal neurotransmitters, epileptic discharges, genetics, neuroendocrine and immune abnormalities, fear reactions akin to the animal defense strategy of tonic immobility, and developmental risk factors warrant further study. There have been advances in demarcating pediatric catatonia as a treatable condition that requires prompt identification. The occurrence of catatonia in autistic patients and the role of overwhelming fear as risk factor support the study of experimental models of developmental impairment and tonic immobility in relation to catatonia.

Learning Objectives:
- Understand examples of how to track both brain circuit function and relate it to behaviors
- Learn status of current efforts to align circuit function with behavioral assays that can be deployed in studies of novel agents

Literature References:
- Dhossche, Wachtel. Catatonia is hidden in plain sight among different pediatric disorders. Pediatric Neurology, 2010, 43:307-315
- Dhossche, Ross, Stoppelbein. The role of deprivation, abuse, and trauma in pediatric catatonia without a clear medical cause. Acta Psychiatr Scand, 2012, 125: 25–32

INDIVIDUAL ABSTRACT:
PHARMACOLOGICAL TREATMENT OF CATATONIA
Gregory Fricchione
Massachusetts General Hospital

The purpose of this talk will be to give a practical summary of an evidence and practice based approach to the pharmacological treatment of the catatonic syndrome based on a review of the clinical literature. Lorazepam remains the first line treatment and a standard approach will be discussed along with other medications that may be tried including other benzodiazepines and GABA a agonists, anti-epileptic drugs, dopaminergic agents and NMDA antagonists. Simple and malignant catatonia will be discussed and the importance of expeditious ECT particularly for the latter condition will be addressed. The challenge of whether to add antipsychotics once catatonia is lysed in severe mental illnesses will be discussed.

Learning Objectives:
- To address particular medication challenges that catatonia presents to clinicians.

Literature References:
- Rosebush PI, Mazurek, MF. Catatonia and its treatment. Schiz Bull 2010; 36: 239-242.
- Fricchione GL, Bush G, Fozdar M, et al: Recognition and treatment of the catatonic syndrome. J Intensive Care Med 1997;12:135-147.
- Mann SC, Caroff SN, Fricchione GL, et al: Malignant catatonia., in Catatonia: from psychopathology to neurobiology. Edited by Caroff SN, Mann SC, Francis A, Fricchione GL. Washington, DC, American Psychiatric Publishing, Inc., 2004, pp 105-120.

INDIVIDUAL ABSTRACT:
DRUG-INDUCED CATATONIA; IMPLICATIONS OF NEW DRUG DEVELOPMENT
Stanley N. Caroff, M.D.
Philadelphia VA Medical Center and the Perelman School of Medicine, University of Pennsylvania

Clinical observation of catatonic and other psychomotor phenomena played a key historical role in the nosology of major psychotic disorders. Over the course of the twentieth century, interest in catatonia waned to the extent that recognition diminished in clinical practice and its status in standardized diagnostic criteria became ambiguous. Paradoxically, awareness of catatonic symptoms arising during the course of pharmacotherapy, including life-threatening disorders such as neuroleptic malignant syndrome and serotonin syndrome, increased during the latter part of the century. Following the introduction of second generation antipsychotic drugs with reduced liability for neurological side effects, the incidence of drug-induced catatonia became obscure. Although the newer drugs may be less likely to induce catatonia, it remains important to recognize drug-induced catatonia to prevent morbidity and mortality, and to better understand pharmacological mechanisms underlying catatonia in association with psychosis. This presentation will review historical trends in the epidemiology and classification of catatonia highlighting evidence on the risk, clinical manifestations, course and outcome of drug-induced catatonia and neuroleptic malignant syndrome, followed by a discussion of the relative impact of different second generation antipsychotic drugs on the occurrence of catatonia among patients receiving treatment for psychosis.

Learning Objectives:
- Participants will be able to discuss the epidemiology, clinical manifestations, course and outcome of drug-induced catatonia
- Participants will be able to discuss the impact of second generation antipsychotic drugs on the incidence and phenomenology of catatonia in the context of psychosis

Literature References:

- Caroff, S.N., Mann, S.C., Campbell, E.C., Sullivan, K.A. Movement disorders associated with atypical antipsychotic drugs. J Clin Psychiatry 63 (suppl 4): 12-19, 2002.
- Caroff SN, Hurford I, Lybrand J, Campbell EC. Movement disorders induced by antipsychotic drugs: implications of the CATIE Schizophrenia Trial. Neurol Clin 2011;29:127–148.
- Caroff,S.N., Mann, S.C., Francis, A., Fricchione, G.: <u>Catatonia: From Psychopathology to Neurobiology</u>, American Psychiatric Press Inc., Washington, D.C, 2004.
- Rogers D., The motor disorders of severe psychiatric illness: A conflict of paradigms. Br J Psychiatry 147:221-232, 1985

GENERAL DISCUSSION
Georgios Petrides
The Zucker Hillside Hospital, Northshore-LIJ Health System

PANEL
8:30 AM – 10:00 AM
PANEL OVERVIEW:
THE SPECTRUM OF MIXED STATES: A BIPOLAR CHOICE STUDY

Andrew A. Nierenberg, M.D.[1], Joseph R. Calabrese, M.D.[2], Michael E. Thase, M.D.[3], Mauricio Tohen, M.D., DrPH, MBA[4], Susan McElroy, M.D.[5]
[1]Massachusetts General Hospital, [2]University Hospitals Case Medical Center, [3]Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center, [4]UTHSCA, [5]Lindner Center of HOPE, The University of Cincinnati College of Medicine

Bipolar disorder frequently presents with a mixture of manic and depressive symptoms (aka "mixity"), but the patterns and correlates of these mixed symptoms have not been studied in detail. The AHRQ Bipolar Comparative Health Outcomes Initiative in Comparative Effectiveness study (Bipolar CHOICE) provides a unique dataset to address the spectrum of "mixity" as well as associated symptoms, comorbid psychiatric, and comorbid medical problems. Bipolar CHOICE compares six months of lithium or quetiapine along with adjunctive personalized treatment for 484 bipolar I and II patients. Participants could enter CHOICE if they had at least mild symptoms and treatment with lithium or quetiapine was appropriate. The diagnoses and symptoms as well as measures of medical comorbid conditions and functioning will be analyzed to assess:

1. Patterns of clustering of manic and depressive symptoms.
2. Depressive symptoms in mania/hypomania.
3. Manic symptoms in bipolar depression.

In addition, we will assess anxiety, irritability, and affective instability as well as retrospective course of bipolar disorder (e.g. age of onset, number and type of episodes, amount of time spent in episode in the past year).

Learning Objectives:
- Understand the distribution of symptoms in bipolar disorder.
- Understand mixed states in bipolar disorder.

INDIVIDUAL ABSTRACT:
CLUSTERING OF DEPRESSIVE AND MANIC SYMPTOMS IN BIPOLAR DISORDER
Michael E. Thase, M.D.

Perelman School of Medicine of the University of Pennsylvania; Philadelphia VA Medical Center
In recent years there has been greater recognition of the prevalence and clinical significance of so called mixed states of bipolar affective disorders. This presentation will examine in incidence and distribution of mixed symptoms in patients presenting with bipolar depressive and hypomanic/manic episodes, drawing upon the pretreatment data of a large group of patients at the time of enrollment into the CHOICE study. It will be shown that many patients present with concurrent symptoms of depression and hypomania/mania and that the incidence of mixed states is highly dependent on the threshold used for classification. In fact, whereas a majority of patients experience some degree of 'mixity', relatively few people actually present for outpatient treatment meeting full syndromal criteria for both major depressive and hypomanic/manic episodes.

Learning Objectives:
- The participant will learn about the history of the concept of mixed bipolar states
- The participant will learn about the prevalences and contingent probabilities of various symptom clusters in bipolar disorder

Literature References:
- Judd LL, Schettler PJ, Akiskal H, Coryell W, Fawcett J, Fiedorowicz JG, Solomon DA, Keller MB. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes.J Affect Disord. 2012 May;138(3):440-8.
- Swann AC, Steinberg JL, Lijffijt M, Moeller GF. Continuum of depressive and manic mixed states in patients with bipolar disorder: quantitative measurement and clinical features.World Psychiatry. 2009 Oct;8(3):166-72.

INDIVIDUAL ABSTRACT:
DEPRESSIVE SYMPTOMS IN MANIA/HYPOMANIA
Joseph R. Calabrese, M.D.
University Hospitals Case Medical Center
In 1921, Kraepelin noted that "cases running a purely manic course begin with marked preference in youth, before the 25th year. He went on to report that "Cases running a purely manic course, which begin after the 55th year, are quite the exception. The frequency of cases, in the narrow sense manic-depressive, also decreases with advancing age, although with small fluctuations, an experience which it would not be difficult to bring into accord with the slighter tendency of advance age to manic attacks." Essentially, Kraepelin's astute observations prompted him to conclude that 'mixity' in bipolar disorder represented the majority of time spent symptomatic during the 2nd and 3rd decades of life, and that during midlife and beyond, the presence of the symptoms of mania became quite unusual. He also noted that after age 60, about 80% of the time spent symptomatic was time spent in pure melancholia. These astute observations by one of the fathers of the phenomenology of manic depression continue to challenge our therapeutic armamentarium. A persuasive literature continues to suggest that pure presentations of mania accompanied by euphoric grandiosity are highly responsive to treatment with lithium and the other antimanic agents, and that the occurrence of depressive symptoms during mania make the illness treatment refractory. The first clear and compelling evidence of this was reported by Alan Swann who led a post hoc analysis of the acute divalproex mania study data which persuasively demonstrated that "Depressive symptoms were associated with

poor antimanic response to lithium" (Bowden et al 1994, Swann et al 1997). Although the presence of depressive symptoms during mania continue to be a challenge, considerable progress has been made and we now have antimanic agents that appear to possess some degree of efficacy in co-occurring depressive symptoms. For example, Tohen and colleagues reported in 2002 that compared with the use of valproate or lithium alone, the addition of olanzapine provided superior efficacy in the treatment of manic and mixed bipolar episodes. This presentation will focus on data obtained from the ongoing Bipolar Trials Network 'CHOICE' Study regarding the phenomenology of depressive symptoms in patients experiencing the symptoms of mania or hypomania and the extent to which patients who present with this particular type of 'mixity' were responsive to treatment regimens that included either lithium or quetiapine.

Learning Objectives:
- Treatment response to regimens of either lithium or quetiapine.

Literature References:
- Bowden C, Brugger A, Swann A, Calabrese J, Janicak P, Petty F, Dilsaver S, Davis J, Rush A, Small J, Garza-Trevino E, Risch S, Goodnick P, Morris D: Efficacy of divalproex vs. lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA 1994 Mar; 271(12):918-24.
- Swann A, Bowden C, Morris D, Calabrese J, Petty F, Small J, Dilsaver S, Davis J: Depression during mania: Treatment response to lithium or divalproex. Arch Gen Psychiatry 1997 Jan; 54(1):37-42.

INDIVIDUAL ABSTRACT:
MANIC/HYPOMANIC SYMPTOMS DURING DEPRESSION
Mauricio Tohen, M.D., DrPH, MBA

This presentation will focus on data obtained from the ongoing Bipolar Trials Network 'CHOICE' Study which is a effectiveness study comparing an atypical antipsychotic (quetiapine) vs. lithium in patients suffering from bipolar disorder. Demographic and clinical features will be described in patients with bipolar depression experiencing mixed features of the opposite pole (mania/hypomania). We will explore if the presence of mixed features in bipolar depression determines the presence of other symptoms or comorbidites. In we will explore in previous course of illness such as type of first episode or episode predominance predicts the presence of mixed features.

The study is unique as it contains close to 500 patients who participated in an effectiveness study which is more likely to be representative to the base population compared to samples recruited for efficacy studies.

Learning Objectives:
- Determine the importance of symptoms of mania in depression.
- Determine the importance of symptoms of depression in mania.

Literature References:
- Tohen M, Wang WV, Leboyer M, Jen KY. Variables as Mediators of Moderators in Predicting Relapse to Any Type of Mood Episode in a Bipolar maintenance Study J Clin Psychiatry 2012 Jul;73(7):e913-e917.
- Tohen M, Khalsa H, Salvatore P, Vieta E, Ravichandran C, Baldessarini R. Two-year Outcomes in First-Episode Psychotic Depression:The McLean-Harvard First-Episode Project Journal of Affective Disorders 2012 Jan;136(1-2):1-8.

GENERAL DISCUSSION

Susan McElroy, M.D.
Lindner Center of HOPE, The University of Cincinnati College of Medicine