Psychiatric Research Society

February 5-8, 2014  ***  Park City, Utah

52nd Annual Meeting

February 5-8, 2014  ***  Park City, Utah
Wednesday, February 5, 2014

7:00 a.m. - 7:30 a.m. Registration and Continental Breakfast

7:30 a.m. - 8:00 a.m. Suicide: Risk Factors Including Psychological Pain and Metallothioneins
William Bunney, M.D., University of California, Irvine, School of Medicine - Page 5

8:00 a.m. - 8:30 a.m. What Are We Treating? Psychiatric Disorders and Medication Use in Adults with Autism Spectrum Disorder
Deborah Bilder, M.D., University of Utah - Page 6

8:30 a.m. - 9:00 a.m. Developing a Smart Phone App to Monitor Mood, Social Rhythms, Sleep and Social Activity: Technology to Support Effective Management of Bipolar Disorder
Ellen Frank, Ph.D., Univ. of Pittsburgh School of Medicine, Western Psychiatric Institute & Clinic - Page 7

9:00 a.m. - 9:15 a.m. Break

9:15 a.m. - 9:45 a.m. An Emerging Genetic Architecture for Major Psychiatric Disorders
John Nurnberger, M.D., Ph.D., Indiana University School of Medicine – Page 8

9:45 a.m. - 10:15 a.m. Novel Association of ADRB2 Gene Polymorphism, in Interaction with Childhood Trauma, and Risk for Adult PTSD
Israel Liberzon, M.D., University of Michigan – Page 9

10:15 a.m. - 10:45 a.m. What Are the Benefits of Integrated Care in Bipolar Disorders? Initial Results from the MedRisk Study
David Kupfer, M.D., University of Pittsburgh School of Medicine Page 10

6:45 p.m. – 7:30 p.m. Reception
Crescent Room

7:30 p.m. – 9:30 p.m. Dinner
Crescent Room
Thursday, February 6, 2014

7:00 a.m. - 7:30 a.m. Registration and Continental Breakfast

7:30 a.m. - 9:30 a.m. President's Symposia

• **Screening for Psychosis & Psychosis Risk: From Specialty Clinics to the General Population**
  Rachel Loewy, Ph.D., University of California, San Francisco – Page 11

• **How Can We Use the Internet and Social Media to Reduce the Duration of Untreated Psychosis**
  Michael Birnbaum, M.D., Zucker Hillside Hospital – Page 12

• **Premorbid/Adolescent Cannabis Use and the Age at Onset of Psychotic Disorders**
  Michael T. Compton, M.D., M.P.H., Lenox Hill Hospital – Page 13

• **Using Mobile Technologies in the Assessment and Treatment of Psychosis**
  Dror Ben Zeev, Ph.D., Dartmouth Psychiatric Research Center – Page 14

9:30 a.m. - 9:45 a.m. Break

9:45 a.m. - 10:15 a.m. **Brain White Matter Development is Associated with a Human-specific Haplotype Increasing the Synthesis of Long Chain Fatty Acids**
  Anil Malhotra, M.D., Hofstra NS-LIJ School of Medicine, Page 15

10:15 a.m. - 10:45 a.m. **The Underutilization of Clozapine**
  John Kane, M.D., The Zucker Hillside Hospital, Page 16

10:45 a.m. - 11:15 a.m. **An Immunotherapeutic Approach to Methamphetamine Addiction Targeting Inflammation and Neuropsychiatric Symptoms**
  Jennifer Loftis, Ph.D., Oregon Health & Science University, Page 17

5:00 p.m. - 6:00 p.m. Business Meeting
Friday, February 7, 2014

7:00 a.m. - 7:30 a.m.  Registration and Continental Breakfast

7:30 a.m. - 8:00 a.m.  Association of Self-reported Change in Alcohol use Behavior with Changes in %CDT, EtG and EtS Levels in Veterans with HCV
Bret Fuller, Ph.D., Oregon Health & Science University, Page 18

8:00 a.m. - 8:30 a.m.  Acid-sensing Ion Channels in the Nucleus Accumbens Contribute to Synaptic Transmission and Inhibit Cocaine-associated Plasticity
John Wemmie, M.D., Ph.D., University of Iowa College of Medicine, Page 19

8:30 a.m. - 9:00 a.m.  Impulsivity: What is the Underlying Circuitry?
Steven Potkin, M.D., University of California, Irvine, Page 20

9:00 a.m. - 9:15 a.m.  Break

9:15 a.m. - 9:45 a.m.  Autonomic Arousal during Waking and Sleep in Male Veterans with PTSD
Walton Roth, M.D., VA Palo Alto HCS, and Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Page 21

9:45 a.m. - 10:15 a.m.  Computer-Delivered Treatment for Substance Use Disorders
Edward Nunes, M.D., Columbia University, Page 22

10:15 a.m. - 10:45 a.m.  Picking a Winner: An Illustration of the Problem Estimating an Effect Size
Martina Pavlicova, Ph.D., Columbia University, Page 23
Saturday, February 8, 2014

7:30 a.m. - 8:00 a.m.  Registration and Continental Breakfast

8:00 a.m. - 10:00 a.m.  Panel Discussion on Duration of Untreated Illness in Psychiatric and Addictive Disorders
Michael Compton, John Kane, David Kupfer & Edward Nunes, Page 24

10:00 a.m.  Conference Concludes
The American Society of Clinical Psychopharmacology has been accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

The American Society of Clinical Psychopharmacology (ASCP) designates this live meeting for a maximum of 10 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

All faculty/planners participating in CME programs sponsored by The American Society of Clinical Psychopharmacology have disclosed any significant financial or other affiliation with commercial organization(s) regulated by the Food and Drug Administration which may have a direct or indirect interest in the subject matter of their presentation. These disclosures will be made available to the audience prior to the presentation.

All speakers have been informed that while they are free to discuss off label uses of any pharmaceuticals they are mentioning, they are to inform the audience when they are doing so.

Support

The American Society of Clinical Psychopharmacology, Inc., and the Psychiatric Research Society would like to acknowledge the generosity of the following companies whose unrestricted educational grants have contributed to the overall quality of this meeting:

Janssen Pharmaceuticals, Inc.
**Wednesday, February 5, 2014**

7:30 a.m. - 8:00 a.m.

**Suicide: Risk Factors Including Psychological Pain and Metallothioneins**

Steven Mee, William Bunney, Blynn G. Bunney, Julie Patterson, Steven Potkin, Christopher Reist, Adolfo Sequeira  
University of California, Irvine, School of Medicine

Suicide represents a major public health problem--38,000 suicides in the US each year. The WHO estimates that 1 million individuals commit suicide worldwide per year. This presentation will review two major risk factors: psychological pain and metallothionein gene expression. Psychological pain has been largely ignored as a critical component of suicidal behavior. Severe psychological or mental pain is defined as an experience of unbearable torment which can be associated with a psychiatric illness. A brief self-rating scale (Mee-Bunney Psychological Pain Assessment Scale [MBP]) was developed to assess the intensity of psychological pain. The scale was used to measure psychological pain in 73 major depressive episode (MDE) patients and 96 controls. In addition to the MBP all subjects were administered the Suicidal Behavior Questionnaire (SBQ). Analyses revealed a significant linear correlation between psychological pain and SBQ suicidality scores. Our finding suggests that psychological pain can be useful in the assessment of risk for suicide. Another risk factor, metallothioneins (MT1,2), was evaluated in postmortem brain tissue from suicides and non-suicides. Results showed that the expression levels of MT1,2 (analyzed by Affymetrix microarrays and confirmed by qPCR) were decreased in the brains of suicidal victims. High cortisol levels have been consistently reported in mood disorder patients. Cortisol increases MT expression which in turn has been shown to have protective effects against the detrimental effects of cortisol. This suggests that suicides may lack a neuroprotective mechanism against the physiological effects of high cortisol.
What Are We Treating? Psychiatric Disorders and Medication Use in Adults with Autism Spectrum Disorder

Deborah Bilder, M.D.¹, Tara Buck, M.D.², Joseph Viskochil, M.Ed.³, Megan Farley, Ph.D.⁴, Hilary Coon, Ph.D.¹, William M. McMahon, M.D.¹
¹University of Utah, Department of Psychiatry; ²University of Utah, Utah Autism Research Program; ³University of Oklahoma School of Community Medicine, Department of Psychiatry; ⁴University of Wisconsin-Madison, Department of Psychiatry

Background: Recognizing the prevalence of co-occurring psychiatric disorders in adults with autism spectrum disorder (ASD) is essential to planning community services and optimizing quality of life. Previous child ASD studies demonstrate high rates (70-80.9%) of psychiatric conditions, though results from adult studies are less consistent. This is the first US study to report psychiatric disorder prevalence and psychotropic medication use in a longitudinal, population-based cohort of adults with ASD.

Objectives: To identify psychiatric disorder prevalence and report community-based psychiatric diagnoses and psychotropic medication use in adults with ASD.

Method: Participants (N=129, 26-54 years old) include those originally identified with DSM III autism (n=107) in the mid-80’s and those later classified with DSM-IV-TR ASD (n=22). Medical/psychiatric histories and Mini Psychiatric Assessment Schedule for Adults with Developmental Disability (Mini PAS-ADD) Clinical Interview were performed.

Results: Psychiatric disorders were present in 73 participants (56.6%); 16 additional participants met criteria for a previous psychiatric disorder. Caregivers reported a psychiatric diagnosis in 44 participants (34.1%). Anxiety disorder had the highest current (39.5%) and lifetime (52.7%) prevalence. Participants with intellectual disability were significantly less likely to have a caregiver-reported diagnosis of anxiety (x²=5.37, p=0.02) or depression (x²=13.18, p<0.001). Seventy-six participants (58.9%) were taking ≥ 1 psychotropic medication; eleven participants (27%) taking atypical antipsychotics were also receiving medication for dyslipidemia and/or diabetes.

Conclusion: Co-occurring psychiatric disorders occur frequently in adults with ASD across the range of intellectual functioning. The discrepancy between community diagnoses and Mini PAS-ADD disorders highlights the challenge of identifying psychiatric conditions in this population.

Correspondence concerning this abstract should be addressed to Deborah Bilder, M.D., Neurobehavior HOME Program, 650 Komas Drive, Suite 200, Salt Lake City, UT 84108; Phone: 801 581-5515; Fax: 801 581-8979; Email: deborah.bilder@hsc.utah.edu.
Developing a Smart Phone App to Monitor Mood, Social Rhythms, Sleep and Social Activity: Technology to Support Effective Management of Bipolar Disorder

Ellen Frank, Mark Matthews, Tanzeem Choudhury, Stephen Voida, Saeed Abdullah
University of Pittsburgh, Cornell University, Trinity College Dublin

Interpersonal and Social Rhythm Therapy (IPSRT), a validated treatment for bipolar disorders helps patients lead lives characterized by greater stability of daily rhythms, using a 5-item paper-and-pencil self-monitoring instrument called the Social Rhythm Metric (SRM). IPSRT has been shown to improve patient outcomes; however, maintaining adherence to self-monitoring remains a major challenge in implementing the treatment. We sought to create a system combining smartphone-based self-report with robust, privacy sensitive automated sensing to help patients maintain stable social rhythms and moods. Specifically, in the development of MoodRhythm we aimed to: (1) design interaction techniques that help patients to assess and reflect on trends in their daily rhythms, social interactions, and mood and motivate them to incorporate the system into their self-care; (2) augment the data traditionally collected through patient journaling; (3) reduce the burden of self-report while dramatically enhancing the validity of the data collected; and (4) explore mechanisms for connecting smartphone data with other health data systems as part of ongoing treatment and a means for alerting clinicians when significant changes in a patient’s mood or behavior are detected. Our current prototype for MoodRhythm uses the phone’s onboard sensors to automatically track sleep and social activity patterns. It also facilitates patient self-report of the 5 SRM items, as well as the creation of individually-tailored patient-specific items and provides reminders to complete them. Initial feedback from experienced IPSRT clinicians and a small cohort of patients with whom MoodRhythm has been tested has been uniformly positive.

9:00 a.m. - 9:15 a.m.  Break
An Emerging Genetic Architecture for Major Psychiatric Disorders

John Nurnberger
Institute of Psychiatric Research, Departments of Psychiatry and Medical and Molecular Genetics, Indiana University School of Medicine

With contributions from investigators around the world, the Psychiatric Genomics Consortium has led efforts to define a genetic architecture for major psychiatric disorders using common variants. Two recent papers from the PGC Cross-Disorder Group (CDG) will be discussed (PGC CDG, 2013; Lee et al, 2013). In the first, five disorders were studied (predominantly schizophrenia (SZ), bipolar disorder (BP), and major depression (MDD). The class of SNPs in calcium channel genes was found to be significantly overrepresented as a whole among high-ranking markers. This defines, for the first time, in a hypothesis-free manner, a neurobiologic basis for the long-observed heritability of major psychiatric disorders. A further paper, now in its final stages of preparation, studies the neurobiology underlying a set of 128 genome-wide significant SNPs associated with SZ, based on a new sample of 35k cases and 47k controls.

These are not the only advances that should be noted. The genetics of ASD is substantially explained by copy number variants (CNVs). A set of CNVs were used to define pathways important in ASD: kinase activity/regulation and GTPase/Ras signaling were relatively specific to ASD; cell proliferation and cell structure pathways were common to ASD and intellectual disability. This work has now been supplemented by studies of gene expression and an expanded examination of CNVs. Sequencing studies have contributed to an appreciation of the combinatorial significance of rare variants of small effect. The underlying importance of these investigations is the identification of significant genes and new neurobiologic mechanisms for psychiatric disorders.

Contact information: jnurnber@iupui.edu; 317-274-8382.
9:45 a.m. - 10:15 a.m.

**Novel Association of ADRB2 Gene Polymorphism, in Interaction with Childhood Trauma, and Risk for Adult PTSD**

Israel Liberzon, M.D., Anthony King, Ph.D., Kerry Ressler, M.D., Ph.D., Lynn Almli, Ph.D., Peng Zhang, Ph.D., Gregory H. Cohen, Marijo Tamburino, M.D., Joseph Calabrese, M.D., Sandro Galea, M.D., MPH

1University of Michigan, 2Emory University, 3Columbia University, 4University of Toledo, 5Case Western University

**Introduction:** Posttraumatic stress disorder (PTSD), while highly prevalent develops only in a subset of trauma-exposed individuals. Genetic risk factors, in interaction with trauma exposure, have been implicated in PTSD vulnerability including FKBP5, 5-HTTLPR and few other genes, however a more comprehensive examination of candidate genes implicated in PTSD, only recently has been initiated.

**Methods:** We examined association of 3644 candidate gene SNPs with PTSD development in interaction with history of childhood trauma, in Ohio Army National Guard longitudinal, cohort (N=715) of predominantly male soldiers of European ancestry. Novel associations were replicated in an independent Grady Trauma Project cohort (N=2803) of predominantly female, African American civilians.

**Results:** We have confirmed the roles of FKBP5 and 5-HTTLPR variants as risk/resilience factors for PTSD development, using GXE interaction models. We also identified novel association of a SNP within the promoter region of ADRB2 gene with PTSD symptoms in interaction with childhood trauma (rs2400707, p=1.02 x 10^-5, significant after Bonferroni correction), controlling for level of life-time trauma exposure. This association was replicated in a predominantly female, African American cohort (p=5.01 x 10^-4).

**Conclusions:** Altered adrenergic/ noradrenergic function has been long believed to play a key role in PTSD development, however direct evidence to this link has been missing. The rs2400707 polymorphism has been linked to function of the adrenergic system but this is the first time the ADRB2 gene linked to PTSD or any psychiatric disorders. These findings have important implication PTSD etiology, chronic pain and stress related comorbidity as well as primary prevention and treatment strategies.

Email: Liberzon@umich.edu, Tel: 734 764-9527
What Are the Benefits of Integrated Care in Bipolar Disorders? Initial Results from the MedRisk Study

David J. Kupfer, Ellen Frank, Martica Hall and Meredith Lotz Wallace
University of Pittsburgh School of Medicine

For more than a decade, we have recognized that individuals with bipolar disorder bear a high burden of medical illnesses and risk factors, primarily of the metabolic syndrome type. These illnesses should be amenable to intervention; however, such intervention is only sporadically received.

To address these concerns we developed an integrated risk reduction intervention (IRRI) that involves a team approach to integrated medical and psychiatric care and a healthy lifestyle modification program. We piloted IRRI in 20 overweight or obese (BMI >24) patients with bipolar I disorder and contrasted their outcomes with those of 20 matched historical controls who received standard psychiatric care (PCO) only. These comparisons suggested meaningful advantages of this approach, leading to the decision to conduct a fully powered RCT, entitled MedRisk, comparing IRRI with optimized psychiatric care with medical management (PCMM) by a nurse/psychiatrist team.

This presentation will focus on results at the end of the acute IRRI intervention, six months after recruiting a population of 114 overweight or obese individuals with a lifetime diagnosis of bipolar I disorder who were euthymic at study entry. Initial analyses indicate significantly greater decreases in body mass index (BMI) among individuals allocated to the IRRI intervention. This change was moderated by both behavioral (sleep amount and timing) and physiologic (inflammatory marker) parameters. Implications of these findings for the management of bipolar I disorder will be discussed.
Self-report screening for psychosis and psychotic-like symptoms is an important tool used by early detection efforts to reduce the duration of untreated psychosis (DUP) and to identify youth experiencing clinical high risk for psychosis (CHR). We will describe a series of validation studies of the Prodromal Questionnaire (PQ) and two brief versions of the measure, tested in a variety of settings in multiple languages and countries: early psychosis clinics, general mental health clinics, university courses, and in a prison population. Accuracy of the instrument compared to clinical interview varies by setting for both sensitivity (71% -90%) and specificity (58%- 87%), as well as positive and negative predictive values and likelihood ratios, with best performance by the brief versions that include information on related distress and impairment. Cutoff selection to maximize accuracy in different settings will be discussed. We will discuss potential uses of web-based screening within broader early psychosis outreach efforts.
This presentation will describe two projects directed towards reducing the duration of untreated psychosis. In our first project, we developed and conducted interviews retrospectively exploring pathways to care and changing patterns of internet and social media use as psychotic symptoms emerged. To date, we have administered a preliminary version of the questionnaire to 32 individuals (mean age 22, 65.6% male, 34.4% female). 31 (96.9%) used social media, 27 (84.4%) used Facebook and participants spent an average of two hours/day using social media. 22 (65.6%) reported a noticeable change in their social media habits as symptoms emerged. 8 (25.0%) reported sharing concerns about their mental state and 5 (15.6%) shared ideas that were clearly psychotic.

In our second project, we explored content of online resources available to youth as psychotic symptoms emerge. Using 18 hypothetical search terms, we searched three of the most popular websites used by youth (Google, Facebook and Twitter) and extracted the first five hits from each. Sites were categorized into those that encouraged help seeking, those that potentially contribute to treatment delay, those that were unrelated to treatment and those with an undetermined impact. An alarmingly few of the first five hits from the top three online resources encourage potentially psychotic youth to seek professional evaluation. The majority of our search results yielded unmonitored chat forums that lacked a unified message. The remainder promoted stigma, normalized potentially psychotic experiences or were completely unrelated to mental health.
Background: Schizophrenia is currently conceptualized as a disorder caused by both genetic predispositions and exposure to stressors or environmental factors, the latter being particularly influential when they occur during childhood and early adolescence. One such environmental factor is cannabis use, especially cannabis use in early adolescence. Several studies have indicated that premorbid/adolescent cannabis use may be associated with an earlier age at onset among those who develop a psychotic disorder, though more definitive evidence is needed.

Methods: In two consecutive National Institute of Mental Health (NIMH)-funded studies, we thoroughly characterized age at onset of psychosis in hospitalized first-episode psychosis patients (n=109 and n=252, respectively), as well as lifetime history of substance use. Analyses determined the associations between premorbid cannabis use and age at onset of psychosis.

Results: In 109 first-episode patients in Atlanta, Georgia, analyses involving change in frequency of use prior to onset indicated that progression to daily cannabis use was associated with increased risk of onset of psychotic symptoms. Similar or even stronger effects were observed when onset of illness/prodromal symptoms was the outcome. The effects of premorbid/adolescent cannabis use were confirmed and further characterized in the second, independent sample of 252 first-episode patients in Atlanta, Georgia and Washington, D.C.

Conclusions: Several first-episode psychosis studies document that the initiation of substance use and abuse typically precedes the onset of psychosis. A number of epidemiological studies have suggested that cannabis use in adolescence is an independent risk factor for the later development of a psychotic disorder; as such, premorbid/adolescent cannabis use is thought to be a component cause of schizophrenia and other psychotic disorders. Convincing evidence now exists showing that premorbid/adolescent cannabis use also hastens the onset of psychosis among those developing a psychotic disorder. Age at onset is a crucial early-course feature as earlier onset is associated with poorer clinical and functional outcomes. Other known predictors of age at onset (gender and family history of psychosis) are not modifiable. Based on the cumulative evidence, preventing or reducing cannabis use among adolescents at elevated risk may delay the onset of psychotic disorders.
Using Mobile Technologies in the Assessment and Treatment of Psychosis

Dror Ben Zeev, Ph.D.
Dartmouth Psychiatric Research Center

Technologies that can facilitate access to evidence-based treatments for psychosis are developing rapidly. Innovative approaches that leverage ubiquitous technology, such as the internet and mobile devices, are already enabling us to transport assessment and treatment for schizophrenia out of the clinic and into the real-time/real-world context in which patients negotiate their daily lives. In the first half of the presentation, Dr. Ben-Zeev will discuss the penetration of mobile technologies among people with severe mental illness and opportunities for mobile health (mHealth) initiatives in this population. In the second half, he will review the development and deployment outcomes of novel smartphone and text-message mobile interventions for schizophrenia.

9:30 a.m. - 9:45 a.m.  Break
Brain White Matter Development is Associated with a Human-specific Haplotype Increasing the Synthesis of Long Chain Fatty Acids

Anil Malhotra¹, Bart Peters¹, Philip Szeszko¹, Pamela DeRosse¹, Todd Lencz¹, Aristotle Voineskos²
¹Zucker Hillside Hospital, Glen Oaks, NY; ²Center for Addiction and Mental Health, Toronto, ON

The genetic and molecular pathways driving human brain white matter (WM) development are only beginning to be discovered. Long chain polyunsaturated fatty acids (LC-PUFAs) have been implicated in myelination in animal models and humans. The biosynthesis of LC-PUFAs is regulated by the fatty acid desaturase (FADS) genes, of which a human-specific haplotype is strongly associated with LC-PUFA concentrations in blood. To investigate the relationship between LC-PUFA synthesis and human brain WM development, we examined whether this FADS haplotype is associated with WM microstructure across the lifespan in healthy individuals aged 9-86 years. Diffusion tensor imaging was performed to measure fractional anisotropy (FA), a putative measure of myelination, of major brain WM tracts. FADS haplotype status was determined with a single nucleotide polymorphism (rs174583) that tags this haplotype. Overall, normal age-related WM differences were observed, including higher FA values in early adulthood compared to childhood, followed by lower FA values across older age ranges.

However, individuals homozygous for the minor allele (associated with lower LC-PUFA concentrations) did not display these normal age-related WM differences. These findings suggest that LC-PUFAs are involved in human brain WM development from childhood to adulthood. This haplotype may play a role in human neurodevelopmental disorders in which both compromised LC-PUFA metabolism and myelination have been implicated, such as schizophrenia.
The Underutilization of Clozapine

John Kane, M.D.
The Zucker Hillside Hospital

It has been 25 years since the publication of “Study 30” demonstrating the superiority of clozapine in carefully selected treatment refractory schizophrenia patients. Despite the development of numerous “atypical” or “second generation” antipsychotics, no other medication has been able to substitute for clozapine despite its safety challenges. Since then the data supporting its superiority for the original indication have expanded, and it was also approved as a treatment for suicidality in schizophrenia.

Guidelines and algorithms developed by a variety of expert bodies are consistent in recommending strong consideration of clozapine after inadequate response to two or more antipsychotic medications.

However, despite estimates that at least one third of patients would qualify for a trial of clozapine, fewer than 1 in 10 such patients receive a trial in the U.S., and approximately 1 in 20 are receiving the drug at any given time. It is also important to note that the U.S. has amongst the lowest rates of clozapine utilization among developed countries.

This presentation will review the most recent surveys regarding knowledge of clozapine and attitudes towards its use on the part of both physicians and patients. In addition, we will review current knowledge regarding safety precautions and frequent premature discontinuation among patients experiencing potentially manageable adverse effects. We will also present data on strategies to encourage/facilitate the appropriate use of clozapine such as academic detailing. Given the high prevalence of antipsychotic polypharmacy in poorly responding patients, we will also discuss the importance of conducting comparative effectiveness trials involving clozapine and polypharmacy.
Methamphetamine (MA) is a highly addictive central nervous system (CNS) psychostimulant that causes long-term damage to regions of the brain that regulate cognitive and psychiatric functions, which makes dependence on the substance particularly challenging to treat. To date, pharmacotherapeutic development for MA addiction has primarily focused on neurotransmitter systems and results from related clinical trials continue to be modest. Further, this strategy may not offer a mechanism for repairing persistent MA induced CNS injury and neuropsychiatric impairments – both vital for successful recovery from MA addiction. In two recent clinical studies, we found altered expression of a network of plasma immune factors and increased problems with anxiety, depression, memory and attention, and quality of life in both active MA users and those in remission from MA dependence, relative to non-dependent controls. Our preclinical data show that an immunotherapeutic approach using partial major histocompatibility complex (MHC)/neuroantigen peptide constructs (pMHCs) has broad anti-inflammatory effects and the potential to safely and effectively treat MA dependence in adults. Taken together, the in vivo data from animal models, including positive impact on cognition, reduced preference for MA consumption, removal of inflammatory cells from the CNS, and repair and regeneration of neuronal tissue, address problems that are central to the underlying pathophysiology of MA addiction recovery and provide strong rationale to advance pMHCs into clinical testing. Plans for a double-blind, placebo-controlled, phase I/II, dose escalation study are in progress in order to test the safety and initial efficacy of our immunotherapeutic approach in adults with MA dependence.

Email address: loftisj@ohsu.edu, jennifer.loftis2@va.gov
Telephone number: 503-220-8262, ext. 57155 (office) or ext. 54725 (laboratory)
Friday, February 7, 2014

7:30 a.m. - 8:00 a.m.

**Association of Self-reported Change in Alcohol use Behavior with Changes in %CDT, EtG and EtS Levels in Veterans with HCV**

Bret Fuller, Ph.D.123, Shira Kern, M.A.4, Jennifer Lofts, Ph.D.123, Eric Dieperink, M.D.5, Peter Hauser, M.D.4

1Research & Development Service, Portland VA Medical Center; 2Department of Psychiatry, Oregon Health & Science University; 3Mental Health and Clinical Neurosciences Division, Portland VA Medical Center; 4Research & Development Service, Long Beach VA Medical Center; 5Research & Development Service, Minneapolis VA Medical Center

Research on Alcohol Use Disorders uses self-report measures such as the AUDIT-C and TLFB. Self-report measures are often not sufficient to accurately measure alcohol use. Biological measures have been implemented in research as correlates of drinking behavior. We aimed to determine the association between self-reported alcohol use with three biological measures associated with alcohol consumption. Carbohydrate deficient transferrin (%CDT), ethyl glucuronide (EtG) and ethyl sulfate (EtS) are biomarkers for the consumption of alcohol, but little data exists regarding accuracy in reflecting self-reported alcohol use. Data from 180 veterans from an ongoing clinical trial of baclofen as a treatment to reduce alcohol consumption and craving in veterans with HCV included a self-report using a 30-day Time Line Follow Back (TLFB) and three biological measures, the %CDT, EtG, EtS. A structural equation model isolated a latent factor of drinking from the TLFB and another latent variable extracted the variance for biological measures and these two latent variables were correlated. The strongest relationships were observed between the previous day drink totals with the EtG and EtS. Relationships were lower for Day 2 and Day 3. Correlations for %CDT with the first day are lower than for the EtG and EtS. Results suggest that the biological measures and self-report measures are robust and correlate moderately. The ethyl-sulfate and %CDT were stronger indicators of drinking than EtG, even though EtG is often used clinically as a measure of alcohol consumption. Early results from the Baclofen trial may also be available to present.

Email address: Bret.Fuller@va.gov
Telephone number: 503-220-8262, ext. 54469 (office)
Acid-sensing ion channels in the nucleus accumbens contribute to synaptic transmission and inhibit cocaine-associated plasticity

University of Iowa College of Medicine

Acid-sensing ion channel 1A (ASIC1A) is abundant in the nucleus accumbens (NAc), a region known for its role in addiction. Because ASIC1A has been previously suggested to promote associative learning, we hypothesized that disrupting ASIC1A in the NAc would reduce drug-associated learning and memory. However, contrary to this hypothesis, we found that disrupting ASIC1A in the NAc increased cocaine-conditioned place preference, suggesting an unexpected role for ASIC1A in addiction-related behavior. Investigating the underlying mechanisms, we identified a novel postsynaptic current during neurotransmission mediated by ASIC1A and ASIC2 and thus well-positioned to regulate synapse structure and function. Consistent with this possibility, disrupting ASIC1A altered dendritic spine density and glutamate receptor function, and increased cocaine-evoked plasticity in AMPA-to-NMDA ratio, all resembling changes previously associated with cocaine-induced behavior. Together, these data suggest ASIC1A inhibits plasticity underlying addiction-related behavior, and raise the possibility of therapies for drug addiction by targeting ASIC-dependent neurotransmission.
Impulsivity: What is the Underlying Circuitry?

Steven Potkin, M.D.
University of California, Irvine

Impulsivity is a very common behavioral characteristic of neuropsychiatric patients that cuts across traditional DSM diagnoses including schizophrenia, bipolar disorder, PTSD, and dementia. Impulsivity underlies or contributes to several symptoms such as suicidality, substance abuse, and violence. Dopamine release in the ventral striatum and medial prefrontal cortex (mPFC) is believed to play a key role in impulsivity (Ohmura et al. J Pharmacol Sci, 2012).

A proposed impulsivity circuit will be presented: prefrontal cortex, hippocampal & amygdala excitatory input (Glu) to the striatum, with modulatory input (dopamine) from midbrain DA neurons (mesolimbic and nigrostriatal). The striatum inhibits (GABA) the ventral pallidum (VP) which in turns modulates the thalamus (via two in series inhibitory GABA neurons). The thalamus sends excitatory input (Glu) to prefrontal cortex completing the loop. The right ventrolateral prefrontal cortex is a key region in regulating impulsivity and response inhibition. Performance on the Iowa Gambling Task, a medialfrontal gyral function, is decreased in both schizophrenia and bipolar patients. Suicide attempts have been linked to impulsivity, and are associated with decreased volume in the frontal and temporal cortices that cut across schizophrenia, schizoaffective, and bipolar diagnoses (Giakoumatos et al, 2013).

Lower FA in the frontal cortex is associated with suicidality in bipolar subjects (Mahon K et al 2012) and bipolar subjects have higher self-reported impulsivity (Reddy et al, 2013) and impairment on the Iowa Gambling Task (Powers et al, 2013) than schizophrenia patients and healthy controls.

Impulsivity in serious mental illness from the perspectives of behavioral performance (stop-signal task) and imaging will be presented. The design of a clinical trial with impulsivity circuitry as an outcome measure will be presented.
9:15 a.m. - 9:45 a.m.

**Autonomic Arousal during Waking and Sleep in Male Veterans with PTSD**

Walton Roth, M.D.
VA Palo Alto HCS and Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

Hyperarousal symptoms are criteria for posttraumatic stress disorder. The elevated arousal of acute stress is generally manifested autonomically by increased heart rate, decreased respiratory sinus arrhythmia, and increased skin conductance level and variability.

56 male veterans with current PTSD were compared to 54 males who had never had PTSD. Participants wore ambulatory devices that recorded electrocardiograms, finger skin conductance, and wrist movement for 22+ hours during daily activities in their normal environments. Sleep and waking periods were established by wrist movement. Heart rate but not the other variables were elevated in participants with PTSD and symptomatic hyperarousal equally during waking and during actigraphic sleep. The length of the sleep periods and estimated sleep efficiency did differ between groups. Group heart rate differences could not be explained by differences in body activity, general PTSD symptom scores, PTSD hyperarousal symptom scores, depression, physical fitness, or antidepressant use.

Thus, among four autonomic measures presumed to indicate hyperarousal, only heart rate showed a group difference. Why HR is elevated while other autonomically regulated measures are unaffected is uncertain. There is evidence from other studies that elevated HRs put PTSD patients at greater risk for cardiovascular disease.
9:45 a.m. - 10:15 a.m.

**Computer-Delivered Treatment for Substance Use Disorders**

Edward V. Nunes, M.D., Aimee N.C. Campbell, Ph.D., Abigail G. Matthews, Ph.D., Maxine Stitzer, Ph.D., Gloria M. Miele, Ph.D., Daniel Polsky, Ph.D., Udi E. Ghitza, Ph.D.

1New York State Psychiatric Institute and Columbia University Medical Center, 2EMMES Inc., 3Johns Hopkins University, 4University of Pennsylvania, 5National Institute on Drug Abuse

**Background:** Drug and alcohol abuse constitutes a major public health problem. Behavioral treatments are effective. However, they face barriers to widespread implementation surrounding costs and logistics of training clinicians and treatment programs to effectively deliver them. Computer-delivered interventions have the potential to surmount some of these barriers, and increase access to quality care. Here, we report a multi-site, community-based effectiveness trial of the Therapeutic Education System, an internet-delivered version of the Community Reinforcement Approach combined with contingency management.

**Method:** Adult men and women (N=507) entering 10 community-based outpatient addiction treatment programs were randomly assigned to a 12-week trial of either treatment as usual (n=252) or treatment-as-usual + Therapeutic Education System (n=255). Therapeutic Education System consists of 62 computer-interactive, multimedia modules, covering skills for achieving and maintaining abstinence, plus prize-based motivational incentives contingent on abstinence and treatment adherence. Treatment-as-usual consisted of usual individual and group counseling at the participating programs. Primary outcomes were (1) abstinence from drugs and heavy drinking, and (2) retention in treatment.

**Results:** Compared to treatment-as-usual, those receiving Therapeutic Education System reduced dropout from treatment (HR=0.72 [95% CI, 0.57-0.92], P=.010), and increased abstinence (OR=1.62 [95% CI: 1.12-2.35], P=.010), an effect that was more pronounced among patients with a positive urine drug and/or breath alcohol screen at study entry (n=228) (OR=2.18 [95% CI: 1.30-3.68], P=.003).

**Implications:** Internet-delivered interventions, such as Therapeutic Education System, have the potential to expand access and improve addiction treatment outcomes. Other types of computer-delivered interventions will be discussed, as well as next steps for research.
Picking a Winner: An Illustration of the Problem Estimating an Effect Size
Martina Pavlicova, Ph.D.¹, Edward V Nunes, M.D.², Aimee N.C. Campbell, Ph.D.², Mei-Chen Hu, Ph.D.²
¹Columbia University, ²New York State Psychiatric Institute and Columbia University Medical Center

Background: Data from small pilot clinical trials are typically used to assert the promise of a new treatment, and to estimate the effect size for planning larger trials. Kraemer and colleagues (Arch Gen Psychiatry 2006) have challenged this practice, based on the likely wide confidence limits of effect size estimates from small studies.

Methods and Results: Here, we illustrate this problem with data from a large (N = 507), 10-site, 2-arm controlled clinical trial of a computer-delivered behavioral intervention for substance dependence, with per-site sample size (N ~ 50 per site) typical of small controlled pilot trials. The primary outcome analysis, on the dichotomous outcome of abstinence from substances, showed a significant main effect favoring the intervention (OR=1.62 [95% CI: 1.12-2.35], P=.010), and a main effect of site, but no site by treatment interaction. The observed and modeled site-wise ORs will be constructed and used as pilot study results to estimate the power of larger study.

Implications: Per-site analysis consisting of confidence intervals and effect estimates, suggests individual sites fail to provide a meaningful estimate of the treatment effect. In a small pilot study, the probability of discovering large effect size of a truly ineffective treatment (Type I Error) is as large as probability of not discovering meaningful effect size of truly effective treatment (Type II Error). The success of future clinical trials should not be based only on single pilot studies, but rather on a confluence of data and opinions from biological, preclinical and clinical levels of evidence.
Saturday, February 8, 2014

7:30 a.m. - 8:00 a.m.  **Registration and Continental Breakfast**

8:00 a.m. - 10:00 a.m.

**Panel Discussion on Duration of Untreated Illness in Psychiatric and Addictive Disorders**
Michael Compton, John Kane, David Kupfer & Edward Nunes

Despite the high prevalence of psychiatric and addictive disorders, many individuals affected by these conditions do not receive needed treatment, and even for those who do, treatment implementation is often delayed for many months or years following illness onset. These inordinate delays in identification and treatment can have enormous personal and public health consequences. Individuals often experience substantial reduction in quality of life and functional ability as a result of untreated illness. In addition, there is evidence that the course of illness, even after the introduction of treatment, can be deleteriously effected by long delays prior to the initiation of treatment. At the same time, reducing the duration of untreated illness is a daunting task involving many domains: public education; self-awareness/insight; stigma; gaps in health care screening, delivery, integration and reimbursement; etc. This panel will bring together a group of experts in different illness categories to discuss contributing factors and potential solutions.

10:00 a.m.  **Conference Concludes**
52nd Annual Psychiatric Research Society Meeting
February 5-8, 2014

All faculty/planners participating in CME programs sponsored by The American Society of Clinical Psychopharmacology have disclosed any significant financial or other affiliation with commercial organization(s) regulated by the Food and Drug Administration which may have a direct or indirect interest in the subject matter of their presentation. These disclosures will be made available to the audience prior to the presentation. All speakers have been informed that while they are free to discuss off label uses of any pharmaceuticals they are mentioning, they are to inform the audience when they are doing so.

Disclosures

William Bunney – Nothing to disclose.

Deborah Bilder – BioMarin Pharmaceuticals


John Nurnberger – Nothing to disclose.

Israel Liberzon – Nothing to disclose.

David Kupfer – American Psychiatric Assn., Psychiatric Assessment, Inc., Copyright Pittsburgh Sleep Quality Index

Rachel Loewy – Nothing to disclose.

Michael L. Birnbaum – Nothing to disclose.

Michael Compton – Nothing to disclose.

Dror Ben Zeev – Nothing to disclose.

Anil Malhotra – Nothing to disclose.

John Kane – Alkermes, BMS, MedAvante, Lilly Genetech, Lundbeck, Intracellular Therapies, Otsuka, Janssen, J&J, Renva and Roche

Jennifer Loftis – Artielle Immunotherapies

Bret Fuller – Nothing to disclose.

John Wemmie – Nothing to disclose.

Steven Potkin – Lundbeck, Otsuka, Novartis, Merck, Sunovion, JNJ, Roche/Genetech, Takeda, BMS, Amgen

Walton Roth – Nothing to disclose.

Edward Nunes – Alkermes/Cephalon, Inc., HealthSim, LLC, Reckitt-Benckiser, Duramed Pharmaceuticals

Martina Pavlicova – Nothing to disclose.