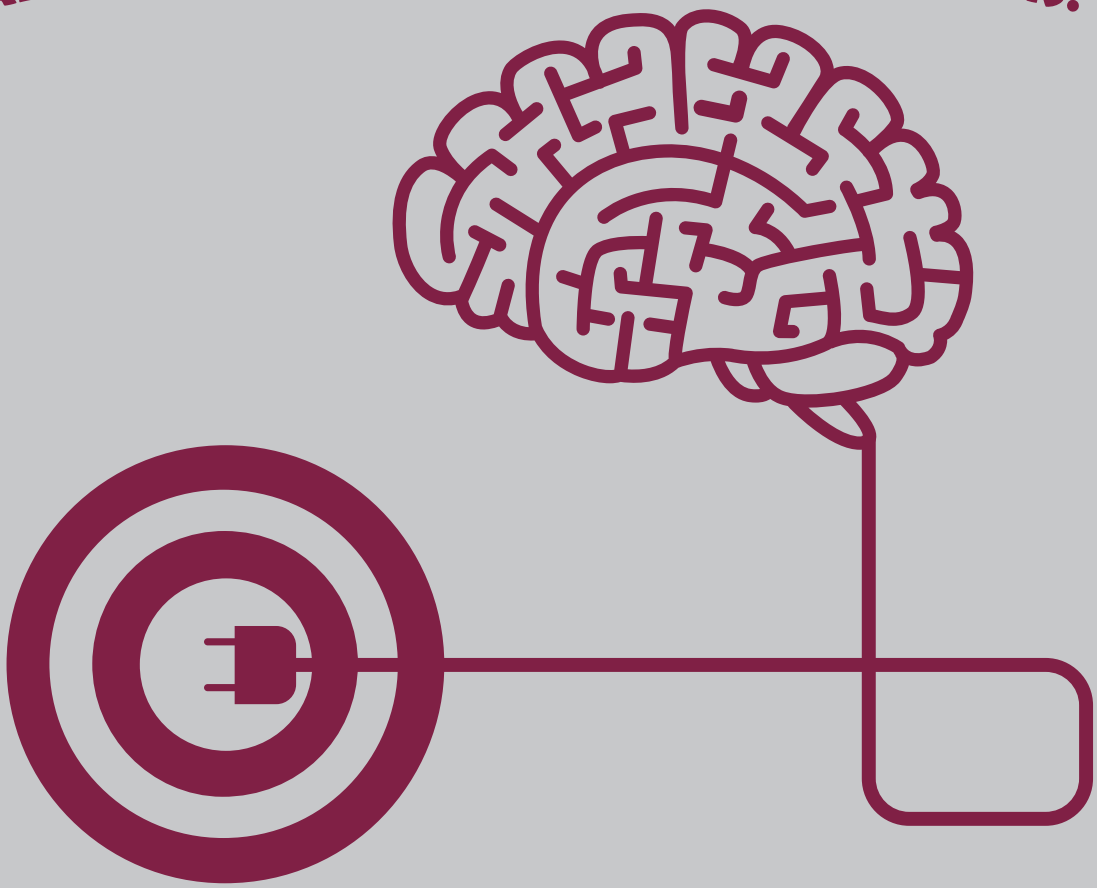
ABSTRACT BOOK

ASCP ANNUAL MEETING

FAIRMONT SCOTTSDALE PRINCESS

MAY 30-JUNE 3, 2016

ANTICIPATING FUTURE INTERVENTIONS:



DISCOVERING NEW TARGETS, INTEGRATIVE BIOMARKERS, AND BEYOND

ASCP
American Society of Clinical Psychopharmacology

www.ASCPP.org

Monday, May 30, 2016

12:00 p.m. - 2:00 p.m.

Latin America Satellite Symposia: An Update on Biomarkers and Clinical Outcomes in Psychiatry

AN UPDATE ON BIOMARKERS AND CLINICAL OUTCOMES IN PSYCHIATRY

Mauricio Tohen, University of New Mexico

Overall Abstract: This symposium will focus on an Update on Biomarkers and Clinical Outcomes in Psychiatry. Mauricio Tohen MD, will discuss Outcome in First Episode Non-Affective Psychosis. The goals of the study are to determine predictors of diagnostic stability in first episode psychosis and to determine time to recovery across non-affective psychoses Antonio Teixeira will describe the complex interactions among temporal lobe epilepsy, depression and low-grade peripheral inflammation, and to evaluate this interaction network as a model for understanding psychiatric disorder. Jair Soares will summarize recent studies that have examined brain mechanisms in bipolar disorder (BD) in children and adolescents. Gustavo Turecki will focus on small non-coding RNAs. He will review data suggesting that microRNAs may be good biomarkers of antidepressant response. Nancy DiazGranados will introduce the behavioral and biological processes involved in the development of alcohol addiction. She will review some recent neuroimaging and genetic findings. The goal is to distinguish some of the genetic variables that contribute to use of alcohol and to the transition from use to abuse and dependence. Carlos Zarate will be the discussant.

SMALL NON-CODING RNA AS PREDICTORS AND MEDIATORS OF ANTIDEPRESSANT RESPONSE

Gustavo Turecki, McGill University

Individual Abstract: Genes can be regulated through the activity of several non-coding RNA (ncRNA) transcripts that act as fine-tuners and on-off switches of gene expression patterns. Among the ncRNAs, microRNAs (miRNAs) are particularly interesting, as they circulate peripherally in exosomes and may act at a distant target. There is increasing evidence suggesting a key role for miRNAs in the regulation of essential processes of brain function, including in psychiatric disorders and their treatments (1). We have recently reported that miR-1202, a primate-specific and brain-enriched miRNA, is down-regulated in the prefrontal cortex of depressed individuals and regulates the expression of the metabotropic glutamate receptor (GRM4) (2). Interestingly, peripheral levels of this miRNA change as a function of antidepressant response. This presentation will discuss the use of microRNAs as potential biomarkers of antidepressant response, discuss most promising findings to date and future avenues.

Learning Objectives:

- Learn about small non-coding RNAs
- Review data suggesting that microRNAs may be good biomarkers of antidepressant response.

Literature References:

- Issler O, Chen A. Determining the role of microRNAs in psychiatric disorders. Nat Rev Neurosci. 2015;16:201-212.
- Lopez JP, Lim R, Cruceanu C, Crapper L, Fasano C, Labonte B, Maussion G, Yang JP, Yerko V, Vigneault E, El Mestikawy S, Mechawar N, Pavlidis P, Turecki G. miR-1202 is a primate-specific and brain-enriched microRNA involved in major depression and antidepressant treatment. Nature medicine. 2014;20:764-768.

OUTCOME IN FIRST EPISODE AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS

Mauricio Tohen, University of New Mexico

Individual Abstract: Background: Early course in contemporary, clinically treated, non-affective psychotic disorders remains incompletely defined.
Methods: We prospectively, repeatedly, and systematically assessed 114 patients hospitalized for a first episode of DSM-IV-TR nonaffective psychotic illness for ≥2 years (1989□1996) using structured (SCID-P, CGI, SANS, SAPS, BPRS-E) and unstructured (best-estimate procedure, life-charting) naturalistic follow-up procedures and survival analysis.

Results: Duration of untreated psychosis (DUP; 22±38 months) was longest with schizophrenia. Within two years, syndromal remission sustained for ≥8 weeks (recovery) was attained by 75 (65.8%) subjects; median latency to syndromal recovery was 9.4 [CI: 5.7–13.3] weeks, and was shorter with cycloid features, initial brief psychosis or schizophreniform disorder, and shorter initial hospitalization. Functional recovery within 2 years was achieved by 28/68 (41.2%), more often without initial mood-psychomotor instability or homicidal ideation. New episodes occurred in 52/114 (45.6%), and were more likely with less affective flattening, younger age, and Caucasian race. Median time to new episodes (43.7 [27.9–70.6] weeks) was earlier with initial first-rank auditory hallucinations, substance abuse, and functional nonrecovery. Diagnosis changed to other nonaffective, schizoaffective, or affective disorders within two-years in 62/108 (57.4%) of cases.

Conclusions: Three-quarters of patients presenting in first-lifetime, nonaffective psychotic episodes achieved recovery within 2 years, but only 41% returned to baseline functioning, and nearly half experienced new episodes. Patients with schizophrenia had the longest duration of untreated psychosis. A majority changed diagnosis, indicating instability of some DSM psychotic-disorder diagnoses

Learning Objectives:

- To determine predictors of diagnostic stability in first episode psychosis.
- To determine time to recovery across non-affective psychoses.

Literature References:

- 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.
- Tohen M, Strakowski SM, Zarate C, Hennen J, Stoll AL, Suppes T, Faedda GL, Cohen BM, Gebre-Medhin P, Baldessarini RJ. The McLean-Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. Biol Psychiatry 2000 Sep;48(6):467-476.

OUTCOME IN FIRST EPISODE NON-AFFECTIVE PSYCHOSIS

of special interest to clinicians

Antonio Teixeira, University of Texas Health Science Center at Houston

Individual Abstract: Patients with temporal lobe epilepsy (TLE) are at an increased risk of mood disorders. Around 30% of patients with TLE followed at referral centers present major depression [1]. Recent studies have proposed a role for inflammatory/immune mechanisms in epilepsy [2]. Immune cells of patients with TLE show an activation profile, mainly in effector T cells, in line with the low-grade peripheral inflammation. For instance, frequency of HLA-DR in CD19+ B cells and regulatory T cells CD4+CD25+Foxp3+ producing IL-10 was higher in TLE when compared with controls [3]. Inflammation also seems to be relevant in the physiopathology of psychiatric disorders, including major depression. We evaluated the peripheral levels of IL-1β, a prototypic pro-inflammatory cytokine, in patients with TLE with depression, patients with TLE without depression and in healthy controls [4]. Levels of IL-1β were significantly higher in patients with TLE with depression than in controls or patients with TLE without depression. IL-1β levels positively correlated with Hamilton Rating Scale for Depression scores. Our current results suggest that at least part of the peripheral immune changes observed in TLE is associated with depression. This finding corroborates the view of systemic impact of major psychiatric disorders, i.e. the presence of low-grade inflammation in patients with major depression. It remains to be determined the influence of treatment on the interaction among TLE, depression and inflammation.

Learning Objectives:

- To describe the complex interactions among temporal lobe epilepsy, depression and low-grade peripheral inflammation.
- To evaluate this interaction network as a model for understanding psychiatric disorder.

Literature References:

- Oliveira GN, Kummer A, Salgado JV, Portela EJ, Sousa-Pereira SR, David AS, Teixeira AL. Psychiatric disorders in temporal lobe epilepsy: an overview from a tertiary service in Brazil. Seizure. 2010 Oct;19(8):479-84.
- Silveira G, de Oliveira AC, Teixeira AL. Insights into inflammation and epilepsy from the basic and clinical sciences. J Clin Neurosci. 2012 Aug;19(8):1071-5.
- Vieira EL, de Oliveira GN, Lessa JM, Gonçalves AP, Oliveira AC, Bauer ME, Sander JW, Cendes F, Teixeira AL. Peripheral leukocyte profile in people with temporal lobe epilepsy reflects the associated proinflammatory state. Brain Behav Immun. 2015 Nov 27. pii: S0889-1591(15)30061-1. doi: 10.1016/j.bbi.2015.11.016.
- Vieira EL, de Oliveira GN, Lessa JM, Gonçalves AP, Sander JW, Cendes F, Teixeira AL. Interleukin-1β plasma levels are associated with depression in temporal lobe epilepsy. Epilepsy Behav. 2015 Dec;53:131-4.

NEUROBIOLOGY OF ALCOHOL USE DISORDERS

Nancy DiazGranados, National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Individual Abstract: The talk will introduce the behavioral and biological processes involved in the development of alcohol addiction. I will review some recent neuroimaging and genetic findings.

Learning Objectives:

- Distinguish some of the genetic variables that contribute to use of alcohol and to the transition from use to abuse and dependence.

- Compare some of the current neuroimaging tasks developed to assess alcohol addiction and discuss their findings.

Literature References:

- Kwako LE, Momenan R, Litten RZ, Koob GF, Goldman D: Addictions Neuroclinical Assessment: A Neuroscience-Based Framework for Addictive Disorders. Biol Psychiatry 2015; In Press.
- Volkow ND, Koob GF, McLellan AT: Neurobiologic Advances from the Brain Disease Model of Addiction. N Engl J Med 2016; 374(4):363-71.

PAEDIATRIC BIPOLAR DISORDER – BRAIN MECHANISMS, EARLY DETECTION AND PROSPECTS FOR NEW INTERVENTIONS

Jair Soares, University of Texas School of Medicine at Houston

Individual Abstract: Objectives: This presentation will summarize recent studies that have examined brain mechanisms in bipolar disorder (BD) in children and adolescents. Methods: We will review data from our research group, as well as literature findings, which demonstrate front-limbic brain abnormalities in kids with BD, as well as unaffected high risk offspring of a BD parent. Studies with various imaging modalities (MRI, MRS, DTI, fMRI) will be discussed, alongside with results from neurocognitive studies.

Results: The available findings indicate FLB abnormalities in children and adolescents with BD, and to a lesser extent, also in the unaffected BD offspring. Key FLB abnormalities seem to start early in illness course and may be proxy markers of vulnerability for BD. Conclusions: FLB pathology is present in patients with BD in the paediatric age range, as well as the high risk paediatric offspring of a BD parent. The possibility that these findings may constitute viable biomarkers of vulnerability for BD and inform future diagnosis and intervention trials is exciting and may transform the course of this illness with much improved outcomes. Acknowledgments: Our study was supported in part by NIH grants MH68766, MH 085667, the John S. Dunn Foundation, and the Pat Rutherford Chair in Psychiatry (UT Health).

Learning Objectives:

- Learn about brain changes possibly involved in bipolar disorder.
- Understand possible implications of such changes for diagnosis, illness course and future therapeutic interventions.

Literature References:

- Mwangi B, Wu MJ, Bauer IE, Modi H, Zeni CP, Zunta-Soares GB, et al. Predictive classification of pediatric bipolar disorder using atlas-based diffusion weighted imaging and support vector machines. Psychiatry Res. 2015;234(2):265-71.
- Bauer IE, Frazier TW, Meyer TD, Youngstrom E, Zunta-Soares GB, Soares JC. Affective Processing in Pediatric Bipolar Disorder and Offspring of Bipolar Parents. J Child Adolesc Psychopharmacol. 2015;25(9):684-90.
- Mwangi B, Spiker D, Zunta-Soares GB, Soares JC. Prediction of pediatric bipolar disorder using neuroanatomical signatures of the amygdala. Bipolar Disord. 2014;16(7):713-21.

2:00 p.m. - 4:00 p.m.

of special interest to clinicians

Latin America Satellite Symposia: New Therapeutic Approaches for Psychiatric Disorders*

NEW THERAPEUTIC APPROACHES FOR PSYCHIATRIC DISORDERS

Rodrigo Machado Vieira, NIMH, NIH

Overall Abstract: Recent developments in psychiatric research are providing new and exciting opportunities for the search of clinically relevant biomarkers and innovative therapeutic approaches. This Symposia will explore the potential integration and usefulness of such current technologies proposed for the evaluation of central and peripheral biomarkers in CNS drug development, which aim to identify hard read-outs and molecular signatures to predict drug response with better accuracy in order to support the path of individualized medicine. In addition, recent advances in the therapeutics of psychiatric disorders based on proof of concept studies targeting new neurotransmitter and neuromodulatory systems will be presented.

EARLY LIFE STRESS IN MOOD DISORDERS: HPA AXIS RESPONSE TO GR AND MR AGONISTS AND ANTAGONISTS

Mario Juruena, King's College London, Institute of Psychiatry, Psychology and Neuroscience

Individual Abstract: Evidence indicates that early life stress (ELS) can induce persistent changes in the HPA axis in adults and that could trigger resistant Unipolar and Bipolar Affective Disorders. These appear to be related to the impairment binding to glucocorticoid (GR) and mineralocorticoid receptors (MR). In the face of GR resistance, an upregulation of mineralocorticoid receptor (MR) is a likely biological response to maintain cortisol concentrations. In our studies affective disorders patients showed a lower salivary cortisol upon waking after placebo compared with controls. Moreover, cortisol awakening responses (CAR) after MR agonist were found to be lower in patients than in controls. CAR after placebo, GR agonist, MR agonist, in a Linear Regression model, in patients with ELS showed differences between placebo vs. MR agonist but not after GR agonist; in patients, without ELS there is difference between placebo vs. MR agonist; but now as well in placebo vs. GR agonist. Our findings indicated that MR activity is impaired in affective patients compared with controls. In patients with ELS, there was suppression only by MR agonist, indicating that patients with ELS are sensitive to MR agonists. In contrast with patients without ELS, we found suppression after both MR and GR agonist. These data suggested that in affective ELS patients there is an imbalance between MR and GR, with MR dysfunction. Suggesting the relevance of the two receptors for functional dysfunction after ELS and suggests novel treatment strategies for a stratified group of patients.

Learning Objectives:

- The aim of this lecture is to review the impact of Early Life Stress (ELS) in HPA axis response to challenges in glucocorticoid (GR) and mineralocorticoid receptors (MR) in Affective Disorders patients.
- These highlights the relevance of the two receptors for the gradual dysfunction after ELS and shows that targeted intervention is possible.

Literature References:

- Juruena MF, Baes CvW, Menezes IC, Graeff FG. Early Life Stress in Depressive Patients: Role of Glucocorticoid Andmineralocorticoid Receptors and Ofhypothalamic-Pituitary-Adrenal Axis Activity. Curr Pharm Des. 2015;21(11):1369-78. PMID: 25564387
- Baes Cv, Martins CMS, Tofoli SMC, Juruena MF. Early Life Stress in Depressive Patients: HPA Axis Response to GR and MR Agonist. Front Psychiatry. 2014 Jan 24;5:2. doi: 10.3389/fpsyt.2014.00002. eCollection 2014. PMID: 24478730

TRANSLATING NEUROTROPHIC AND PLASTICITY PATHWAYS INTO NEW TREATMENTS FOR MOOD DISORDERS

Rodrigo Machado Vieira, NIMH, NIH

Individual Abstract: This study investigated dysfunctions of critical neurotrophic, cellular plasticity, resilience pathways and neuroprotective processes at a molecular and cellular level. Lithium was used as the proof of concept agent to study these targets at multiple levels using a wide range of translational and tools and technologies (MRI, 1H and 7Li MRS, GWAS, proteomics, transcriptomics). This multimodal approach allowed the identification of therapeutic targets of mood stabilizers resulted from a physiological restoration at these altered pathways and processes through a wide range of biochemical and molecular effects associated with antidepressant response. These findings suggest that non-remitters may not transport lithium properly to the brain, which may underlie treatment resistance to lithium in BD. They also reinforce a role for ACC glutamate-glutamine cycling, GSK-3 and myoinositol pathway as key targets for lithium's therapeutic effects in BD.

Learning Objectives:

- To describe targets in plasticity and resilience cellular pathways involved in the pathophysiology of mood disorders based on the studies with lithium.
- To understand predictors of response and surrogate outcomes in depression and mania associated with lithium and other neuroprotective agents in mood disorders. To plan studies (clinical and translational) to test key therapeutic targets within this system based on the findings with lithium, the gold standard and proof of concept neuroprotective agent in mood disorders and beyond.

Literature References:

- Machado-Vieira R, Otaduy MC, Zanetti MV, De Sousa RT, Dias VV, Leite CC, Forlenza OV, Busatto GF, Soares JC, Gattaz WF. A Selective Association between Central and Peripheral Lithium Levels in Remitters in Bipolar Depression: A 3T-(7) Li Magnetic Resonance Spectroscopy Study. Acta Psychiatr Scand. 2015 Oct 29. doi: 10.1111/acps.12511. [Epub ahead of print] PubMed PMID: 26513535.
- Machado-Vieira R, Gattaz WF, Zanetti MV, De Sousa RT, Carvalho AF, Soeiro-de-Souza MG, Leite CC, Otaduy MC. A Longitudinal (6-week) 3T (1) H-MRS Study on the Effects of Lithium Treatment on Anterior Cingulate Cortex Metabolites in Bipolar Depression. Eur Neuropsychopharmacol. 2015 Dec;25(12):2311-7. doi: 10.1016/j.euroneuro.2015.08.023. Epub 2015 Sep 25. PubMed PMID: 26428274.

NEW TREATMENTS FOR ALCOHOLISM: A FOCUS ON THE GUT-LIVER-BRAIN AXIS

Lorenzo Leggio, NIH, CPN Section, NIDA, NIAAA

Individual Abstract: The gut-liver-brain axis may play a key role in a variety of psychiatric diseases, including alcohol and substance use disorders. Within the gut-liver-brain axis, a number of peptide hormones secreted by gastrointestinal tissues control food consumption though their central nervous system effects on hunger, satiety and energy metabolism and storage. Recent research suggests that these appetitive hormones can also influence the consumption of addictive substances, including alcohol. A better understanding of the neurobiology of appetitive hormones may lead to improved treatments not only for obesity and eating disorders, but also for alcohol and substance use disorders. Dr. Leggio will provide an example of this approach, primarily based on work conducted in his lab, where recently published and ongoing efforts are directed toward a better understanding of the role of the appetitive hormone ghrelin as a potential novel target for the treatment of alcoholism.

Learning Objectives:

- Understand the role of pharmacological treatments for alcohol and substance use disorders.
- Understand the potential role of studying the gut-liver-brain axis as a novel approach to discover and develop new treatments for addictions.

Literature References:

- Kenna GA, Swift RM, Hillemacher T, Leggio L. The relationship of appetitive, reproductive and posterior pituitary hormones to alcoholism and craving in humans. Neuropsychol Rev. 2012;22:211-28
- Leggio L, Zywiak WH, Fricchione SR, Edwards SM, de la Monte SM, Swift RM, Kenna GA. Intravenous ghrelin administration increases alcohol craving in alcohol-dependent heavy drinkers: a preliminary investigation. Biol Psychiatry. 2014;76:734-41

PROMISING MEDICATIONS TO TREAT SUBSTANCE USE DISORDERS

Ivan Montoya, DHHS/National Institute on Drug Abuse

Individual Abstract: Illicit drug use affects the health and well-being of millions of Americans and is a significant public health burden. It is estimated that 7 million Americans have an illicit drug use disorder. There are approximately 4.2 million with marijuana use disorder, 2.5 with opioid use disorder, 900,000 with cocaine, and half a million with heroin use disorder. Currently, there are no FDA-approved medications to treat stimulant (cocaine and methamphetamine) and marijuana use disorders. The only drug use disorders with FDA-approved pharmacotherapies are opioid and nicotine use disorders, but the one-year abstinence rates are less than 20%. Therefore, there is a critical need to develop safe and effective interventions to treat substance use disorders (SUD). Recent advances in understanding the neurobiology of addiction are providing information about new pharmacological targets and the opportunity to develop new pharmacotherapies. The National Institute on Drug Abuse (NIDA) has an active program of discovery and development of therapeutics for SUDs. Some of the research approaches included compounds modulating dopamine, nicotinic, opioid, glutamate, GABA and other brain pathways. NIDA also has a program of development of biologics such as vaccines, monoclonal antibodies, and enzymes as therapeutics aimed at limiting the access of drugs to the brain. The purpose of this symposium is to provide a general overview of the most promising therapeutic approaches for SUDs in the continuum of translation from basic to clinical research.

Learning Objectives:

At the end of the presentations, the audience will:

- Learn about the new targets and compounds that are being developed to treat SUDs.
- Gain knowledge about the medications and biologics that appear most promising for the treatment of SUDs.

Literature References:

- Montoya ID, Vocci F.: Novel medications to treat addictive disorders. Curr Psychiatry Rep. 2008 Oct;10(5):392-8. Review.
- Skolnick P, Volkow ND.: Addiction therapeutics: obstacles and opportunities. Biol Psychiatry. 2012 Dec 1;72(11):890-1

NEW GLUTAMATE MODULATORS FOR MOOD DISORDERS

Carlos Zarate, National Institute of Mental Health

Individual Abstract: All currently approved antidepressant medications for major depressive disorder (MDD) and bipolar disorder act primarily on the monoaminergic system and have varying affinities for serotonergic, noradrenergic, and/or dopaminergic receptors. Unfortunately, these pharmacological agents are efficacious in approximately two-thirds of patients. Glutamate is the major excitatory neurotransmitter in the central nervous system, and the glutamatergic system has been implicated in the pathophysiology of mood disorders. In this lecture, I will review the putative involvement of the glutamate receptor subtypes-N-methyl-D-aspartate (NMDA) and its allosteric sites, α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid (AMPA), kainate, and the group I, II, and III metabotropic glutamate receptors (mGluRs)-in the development of novel and more effective treatments for MDD as well as preclinical and clinical trials of drugs targeting these receptors. The rapid and robust antidepressant effects of ketamine-an NMDA receptor antagonist-have been consistently replicated in multiple trials. Other glutamatergic drugs have been studied with varying success. Here, I highlight some of the most interesting results, including: 1) repeated oral, intramuscular, and sublingual ketamine appears to be less robustly effective than intravenous ketamine, but also causes fewer significant adverse effects; 2) the glycine partial agonist GLYX-13 appears to be effective both as monotherapy and adjunctive treatment in the treatment of MDD. An oral analogue, NRX-1074, is currently under investigation; 3) glycine antagonists, and 4) mGluR modulators targeting mGluR5 have demonstrated convincing preclinical results. These targets may be of substantial interest in defining future directions in drug development, as well as in developing the next generation of therapeutic agents for the treatment of mood disorders. Overall, further study of these and similar drugs may lead to a better understanding of relevant and clinically useful drug targets in the treatment of these devastating illnesses.

Learning Objectives:

- The participant will understand the rationale for developing glutamatergic modulators for mood disorders.
- The participant will understand what are the current glutamatergic modulators being developed for depression.

Literature References:

- Machado-Vieira R, Henter ID, Zarate CA Jr. New targets for rapid antidepressant action. Prog Neurobiol, 2015 [Epub ahead of print]. PubMed:26724279.
- Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CA, Jr., Charney DS. Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of

depression: ketamine and other compounds. Annu Rev Pharmacol. 2014;54:119-139. PubMed: 24392693.

Tuesday, May 31, 2016

9:00 a.m. - 10:30 a.m.

Tuesday Morning Panel Sessions*

ADHD IN ADULTS WITH A FOCUS ON ASSESSMENT, COMORBIDITY AND ASSOCIATED FEATURES*

Frederick Reimherr, University of Utah School of Medicine

Overall Abstract: ADHD is a common disorder with a high degree of comorbidity for disorders in axis I and II. While dysregulation of attention is the symptom area central to our concept, impulsivity, hyperactivity, temper and other forms of emotional dysregulation are also common and highly debilitating. This presentation will look at current research into the complex interactions between ADHD and common comorbidities including; violence, personality disorder, and emotional dysregulation. Further, Dr. Sumner will address traditional forms of evaluating ADHD and compare their benefits with the newer "objective" assessments. It is hoped that this presentation will increase the listeners the ability to assess, understand and treat patients with this complex disorder.
Emotional Dysregulation – a Distinct Subtype of Adult ADHD

Much recent research describes the importance of emotional symptoms and comorbidity in ADHD. The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) provides a tool to assess these symptoms in adults with ADHD. It assesses a range of adult ADHD symptoms which load on two factors: inattentive and emotional dysregulation. Marked impairment on the emotional factor emotional domains reflected a symptom severity level equivalent to that of the inattentive factor leading to the definition of ADHD emotional dysregulation presentation subjects. These subjects showed more childhood ADHD symptoms, adult symptoms of oppositional defiant disorder, and evidence of personality disorder.

Learning Objectives:

- Attendees will have a greater understanding of the complexity of symptoms for adults with ADHD.
- Attendees will have greater ability to identify which symptoms are part of ADHD versus evidence of comorbidity.

ADHD IN ADULTS WITH A FOCUS ON COMORBIDITY AND ASSOCIATED FEATURES

Calvin Sumner, NCS Pearson - Clinical Assessment

Individual Abstract: Active clinicians recognize the difficulty involved in fully assessing the symptoms of ADHD patients especially given the symptoms associated with comorbidity as well as the anxiety caused by its impact upon social/family/work. Research and reality are

disconnected by the complexity that real patients display and the challenge to fully assess the impact the disorder has upon each patient. Researchers and clinicians need to better understand the relative benefits of various measures. The recent development of objective/physiological measures contributes very different information than the typical symptom checklists. They appear to have potential to identify those who are feigning the disorder and they may also inform us on the mystery of why hyperactivity seems less common during adulthood.

Learning Objectives:

- Participants will appreciate the complexities in assessment of an adult for potential ADHD, including the possibility that the adult is misrepresenting ADHD symptoms.
- Participants will be able to integrate new assessment technologies into their evaluation of an adult for potential ADHD.

Literature References:

- Booksh, R. L., Pella, R. D., Singh, A. N., & Gouvier, W. D. (2010). Ability of college students to simulate ADHD on objective measures of attention. Journal of Attention Disorders, 13, 325-338.
- Sollman, M. J., Ranseen, J. D., & Berry, D. T. (2010). Detection of feigned ADHD in college students. Psychological Assessment, 22, 325-335.

VIOLENCE IN ADULT ADHD - THE ROLE OF ADHD ON TYPE OF AGGRESSION

Florence Philipp-Wiegmann, Institute for Forensic Psychology and Psychiatry, Saarland Universität, Homburg/Saar, Germany

Individual Abstract: Disruptive behavior within forensic clinical samples includes psychopathological and behavioral constructs like aggression, impulsivity, violence, antisociality and psychopathy and is often closely related with diagnostic categories like conduct disorder, Attention-Deficit/Hyperactivity Disorder and antisocial personality disorder. During childhood, ADHD is often accompanied by oppositional defiant disorder and conduct disorder, similarly ADHD is prevalent in offender populations. A common concern is the risk of violent behavior even though violence is not common for adults with ADHD. It is becoming clear that the psychopathology of ADHD and psychopathy are two different concepts which show little overlap. This talk will describe the actual rates of violence within an ADHD sample alongside the childhood attributes which are associated with adult violence. As hyperactive-impulsive traits are core symptoms of ADHD, it has been hypothesized that reactive-impulsive violence is more likely related to ADHD psychopathology than proactive-instrumental violence (e.g. within prison samples). The response to treatment will also be discussed.

Learning Objectives:

- Audience members will be able to describe ADHD as a risk factor of disruptive behavior and the relationship of ADHD to aggression.
- Audience members will be able to describe the role of ADHD on type of aggression and the prevalence of ADHD within prison samples.

Literature References:

- Retz, W., Rösler, M. (2009). The relation of ADHD and violent aggression: What can we learn from epidemiological and genetic studies? International Journal of Law and Psychiatry,32, 235-243.

of special interest to clinicians

- Retz, W., Rösler, M. (2010). Association of ADHD with reactive and proactive violent behavior in a forensic population. ADHD Attention Deficit and Hyperactivity Disorders, 2, 195-202.

PERSONALITY DISORDER IN ADULT ADHD

Thomas Gift, University of Rochester

Individual Abstract: Multiple reports suggest that personality disorders are found in about half of adults diagnosed with ADHD. However, the consequences of this observation warrant further exploration.

To assess manifestations of personality disorder, as well as personality traits, in adults with ADHD data were analyzed from two methylphenidate clinical trials, both with a randomized, double-blind, crossover followed by an open-label phase. Each study included a careful evaluation of personality disorder diagnosis & traits using the Wisconsin Personality Inventory (WISPI-IV) and the SCID-II, with assessment at baseline and following treatment. Subjects experienced significant improvement in both ADHD symptoms ($p<.001$) and WISPI-IV scores (range $p=.03$ to $p=.001$) between baseline and the open-label endpoint. The presence of more than one personality disorder diagnosis was associated with poorer acute treatment response, as were a greater number or personality disorder traits. These findings suggest that personality traits and disorders may influence adult subjects' response to stimulant treatment of ADHD and may complicate the conduct of clinical trials investigating adult ADHD patients.

Learning Objectives:

- Audience members will be able to describe aspects of personality associated with ADHD symptoms in adults.
- Audience members will be able to describe personality traits associated with attrition from studies of pharmacotherapy of ADHD in adults.

Literature References:

- Marchant BK, Reimherr FW, Robison D, Robison RJ, Wender PW. Psychometric properties of the Wender- Reimherr Adult Attention Deficit Disorder Scale. Psychol Assess. 2013;25:942-950.
- Reimherr FW, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. Biol Psychiatry. 2005;58:125-131.

PUBLIC-PRIVATE PARTNERSHIPS TO DEVELOP MEDICATIONS FOR ALCOHOL USE DISORDER: RECENT SUCCESSES AND NEW OPPORTUNITIES FOR COLLABORATION WITH NIAAA

Raye Litten, NIAAA

Overall Abstract: Notable advances have been made in medications development to treat alcohol use disorder (AUD). Currently, three medications have been approved by the Food and Drug Administration (FDA) to treat alcohol dependence: disulfiram, oral and long-acting injectable naltrexone, and acamprosate. In addition, nalmefene was recently approved in Europe for alcohol dependence. Still, due to the heterogeneity of AUD, these medications are not effective for everyone. A top priority of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to develop more efficacious and safe medications, offering clinicians

a menu of medication choices to treat this complex disorder. Dr. Raye Litten will highlight recent NIAAA programs that enhance the speed and predictability of medications development and, importantly, facilitate new partnerships with the pharmaceutical industry. One such program is the successful NIAAA Clinical Investigations Group (NCIG), which has completed 4 multisite alcohol pharmacotherapy trials, averaging only one and half years per trial. Three NCIG trials have involved pharmaceutical partners. Results of two NCIG trials will be presented. A third NCIG trial (currently in-progress) being conducted in collaboration with XenoPort, Inc. will also be described. Dr. Daniel Falk will present the results of a multi-site varenicline trial of 200 alcohol dependent patients, both smokers and non-smokers. Compared to placebo, varenicline significantly decreased several measures of alcohol consumption, alcohol craving, and smoking (among smokers). Moreover, varenicline appeared to be more efficacious in certain subgroups, particularly in those who reduced their smoking and in "less severe" alcohol dependent patients. Megan Ryan will present results of the latest multi-site trial of ABT-436, a novel compound that acts to block the V1b receptors, in 148 alcohol dependent patients. This trial was carried out via a Cooperative Research and Development Agreement (CRADA) with AbbVie Inc. Compared to placebo, ABT-436 significantly reduced the percentage of days abstinent; and non-significant trend emerged for reduction in the percentage of heavy drinking days. In a subgroup analysis, patients with relatively high stress appeared to respond better to ABT-436. Finally, the compound also significantly reduced the number of cigarettes per week in the alcohol dependent smoking group.

Learning Objectives:

- Describe new opportunities for public-private partnerships to develop medications for alcohol use disorder.
- Review results of a clinical trial of varenicline in alcohol dependent smokers and non-smokers.
- Discuss results of a clinical trial of ABT-436, a novel compound that acts to block the V1b receptors, in alcohol dependent patients.

INFRASTRUCTURE TO FACILITATE DRUG DEVELOPMENT: PUBLIC-PRIVATE PARTNERSHIPS

Raye Litten, NIAAA

Individual Abstract: Drug development is difficult and challenging, particularly for central nervous system (CNS) compounds. It takes 18 years from discovery to market to develop CNS candidate compounds, 4.5 years longer than non-CNS compounds. It is estimated that the cost from discovery through launch is at least $1.8 billion dollars. These high costs are caused, in part, to the many compound failures, particularly in human studies. For example, only 46% of new CNS compound succeed in pivotal clinical trials, compared to 66 % for other non-CNS compounds. The goal of National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to develop approaches along the drug development pipeline to make drug development faster, more predictable and less expensive. To help accomplish this goal, NIAAA has initiated three programs: a standardized animal model screening program, a standardized human laboratory program, and a network of sites to conduct clinical trials. All three programs encourage pharmaceutical partnerships. The alcohol field is fortunate to have a variety of alcohol animal models that can be used to screen promising compounds. Standardized animal models were developed by NIAAA to avoid the variability in the methodology of paradigms and animal species and strains across academic sites. To validate

the standardized animal models, reference medications, compounds that already have undergone clinical evaluation, were tested for specific patterns of efficacy across the standardized model. The same approach is also being developed using human laboratory paradigms. Human laboratory studies can be carried out faster and with less expense than clinical trials. Finally, NIAAA has established a network of sites to conduct alcohol clinical trials in a turnaround time of less than 1.5 years. Within the past 8 years, four multisite clinical trials have been completed and recruitment of a fifth trial is over one-third completed. NIAAA formed a partnership with a pharmaceutical company in three of the clinical trials. Developing a solid infrastructure to accelerate promising medications through the drug development pipeline and establishing partnerships with pharmaceutical industry are high priorities for NIAAA for the next decade.

Learning Objectives:

- Discuss the advantages of validating screening models to improve the efficiency of drug development.
- Review the results of using an established network of clinical sites to conduct alcohol clinical trials.

Literature References:

- Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF. Heterogeneity of Alcohol Use Disorder: Understanding Mechanisms to Advance Personalized Treatment. Alcohol Clin Exp Res 2015; 39:579-584.
- Litten RZ, Ryan M, Falk D, Fertig J. Alcohol Medications Development: Advantages and Caveats of Government/Academia Collaborating with the Pharmaceutical Industry. Alcohol Clin Exp Res 2014; 38:1196-1199.
- Litten RZ, Egli M, Heilig M, Cui C, Fertig JB, Ryan ML, Falk DE, Moss H, Huebner R, Noronha A. Medications development to treat alcohol dependence: a vision for the next decade. Addict Biol 2012; 17:513-527.

MODERATORS OF VARENICLINE TREATMENT EFFECTS IN A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL FOR ALCOHOL DEPENDENCE: AN EXPLORATORY ANALYSIS

Daniel Falk, NIAAA/NIH

Individual Abstract: Objectives: To explore whether varenicline (Chantix) showed more efficacy in treating certain subgroups of patients. In a recent multisite trial, varenicline was shown to be effective in reducing drinking in alcohol-dependent patients, both smokers and nonsmokers. Given the heterogeneity among alcohol-dependent patients, secondary analyses were conducted to determine whether certain subgroups responded more favorably than others to treatment with varenicline. Methods: Data were drawn from a phase 2 randomized, double-blind, placebo-controlled multisite 13-week trial of varenicline in alcohol dependent patients (Litten et al., 2013). Seventeen moderator variables were selected for exploratory testing on the basis of theoretical and scientific interest. Results: Of the 17 moderator variables assessed, 4 were statistically significant, including cigarettes per day reduction, treatment drinking goal, years drinking regularly, and age of the patient. Two other variables—the type of adverse events experienced by patients and the severity of alcohol-related consequences—seemed to moderate the varenicline treatment effect at borderline statistical significance. Individuals who reduced the number of cigarettes per day experienced a significant effect from varenicline in reducing drinking, whereas those who did not change or who increased their number of cigarettes observed no beneficial effect. Reviewing the

moderators related to severity, varenicline seemed to have greater efficacy than placebo among less severely dependent patients. Conclusions: Varenicline seems to be more efficacious in certain subgroups, particularly in those who reduced their smoking and in the "less severe" patient. Additional studies are warranted to confirm the results of these exploratory analyses.

Learning Objectives:

- Participants will gain familiarity of a significant pharmacotherapy trial to treat alcohol use disorder, conducted by the NIAAA Clinical Investigations Group (NCIG) program.
- Participants will gain an understanding of which types of patients best respond to varenicline.

Literature References:

- Falk DE, Castle IJ, Ryan M, Fertig J, Litten RZ. 2015. Moderators of varenicline treatment effects in a double-blind, placebo-controlled trial for alcohol dependence: an exploratory analysis. J Addict Med 9(4):296-303.
- Litten, RZ, Ryan, ML, Fertig, JB, Falk, DE, Johnson, B, Dunn, KE, Green, AI, Pettinati, HM, Ciraulo, DA, Sarid-Segal, O, Kampman, K, Brunette, MF, Strain, EC, Tiouririne, NA, Ransom, J, Scott, C, Stout, R, and the National Institute on Alcohol Abuse and Alcoholism Clinical Investigations Group (NCIG) Study Group. 2013. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med 7(4):277–286.

A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL ASSESSING THE EFFICACY OF ABT-436 (V1B ANTAGONIST) FOR ALCOHOL DEPENDENCE

Megan Ryan, NIAAA

Individual Abstract: Alcohol Use Disorder (AUD) has been linked to dysregulation of the brain regions that mediate stress, producing a negative emotional state that can lead to chronic relapsing behavior. Vasopressin, a neuropeptide that acts on the V1b receptors located centrally in the brain, is believe to regulation stress, anxiety, and alcohol and substance abuse-like behaviors. In this study, ABT-436, a novel compound that acts to block the V1b receptor, was evaluated in alcohol dependent patients for both efficacy and safety. This is the first clinical trial conducted with this compound and the first multisite alcohol trial conducted in the US that targets the stress system. Men and women (n = 148) meeting the criteria for alcohol dependence were recruited across 4 clinical sites. Patients received double-blind ABT-436 or placebo and a computerized behavioral intervention. ABT-436 was titrated from 200 mg/day on day 1 to 400 mg/day for days 2-7, and then maintained on 800 mg/day for weeks 2-12. The primary outcome, percent heavy drinking days, did not significantly differ between the ABT-436 and placebo groups, although a reduction was observed in the ABT-436 group compared to the placebo group (31.1 versus 37.6, respectively; p = 0.172). While there were no significant differences in drinks per day and drinks per drinking day, the percent days abstinent was significantly increased in ABT-436 group compared to the placebo group (51.2 versus 41.6, respectively; p =0.036). In a subgroup analysis, patients who were "high stress" at baseline appeared to respond better to ABT-436. Patients treated with ABT-436 also significantly reduced the number of cigarettes per week, but not alcohol craving or alcohol-related consequences. ABT-436 was well tolerated, with diarrhea (mild to moderate severity) being the most common side effect (50.7 percent versus 19.7 percent for placebo; p<.001). In sum, blocking the V1b receptor with

ABT-436 appears to alter the frequency of drinking without significantly reducing the amount of drinking once drinking has occurred. There is evidence that AUD patients with high stress respond more favorably to ABT-436 in reducing both the frequencies of drinking days and heavy drinking days. Interestingly smoking was also reduced, demonstrating the overlap between drinking and smoking. Further studies are warranted in exploring this target as well as other targets within the stress system.

Learning Objectives:

- Efficacy of ABT-436, a V1b antagonist to treat alcohol dependence.
- Study design used to evaluate a medication targeting the stress system.

Literature References:

- Koob G: A Role of Brain Stress Systems in Addiction. Neuron 2008; 59:11-34
- Edwards S, Guerrero M, Ghoneim OM, Roberts E, Koob G: Evidence that vasopressin V1b receptors mediate the transition to excessive drinking in ethanol-dependent rats. Addict Biol 2011; 17:76-85

MOBILE HEALTH: REAL-TIME MONITORING IN BIPOLAR DISORDER AND ADDICTIONS*

Erika Saunders, Penn State College of Medicine, Penn State Milton S. Hershey Medical Center

Overall Abstract: Personal device technology has facilitated gathering data in real-time to identify symptoms and behaviors that put individuals at risk for emergent worsening of clinical state. Here, we discuss three studies that use mobile devices to monitor health, and use data to predict outcome. 1) PRIORI (predicting individual outcomes for rapid intervention) is a mobile health based technology that captures outgoing speech from telephone conversations on a smartphone in order to analyze the acoustic patterns in association with mood symptom and severity estimations. Additional meta-data captured from the daily use of the device are also gathered for analyses. Currently the PRIORI project has 47 individuals that have used the system and have 39,780 telephone calls in the database, there are 1,230 calls with clinical assessments associated with a specific call. Participants have used PRIORI continuously for up to one year. Analysis of acoustic features finds an average AUC of 0.7 in associating with the clinical state at the time of the assessment. This suggests that acoustic features gathered using mobile devices may be useful in predicting mood states. 2) In a two week, parallel group, observational study of a mood and stress survey delivered through auto-generated or self-generated manner on smartphones in bipolar disorder and healthy control participants, completion rates overall and completion of auto-generated surveys did not differ between groups. The BD group had significantly lower median mood and energy score than the HC group, and significantly higher variability of mood, speed of thoughts and impulsivity scores over the course of 14 days than HC, while energy and social stress scores did not differ. 3) During the post-withdrawal period from prescription opiates, low positive affect (PA) is likely to contribute to craving – and risk of relapse - but has received little attention in clinical research. Smart phones were programmed to collect ecological momentary assessment (EMA) of positive affect (PA), negative affect (NA), and craving 4x daily for 12 days among patients in residential treatment. Within-person and within-day associations between PA, NA, and craving were examined using multilevel models. Low PA was associated with greater craving for those individuals who experienced, on average, low mean PA throughout the study. Individuals experiencing, on average, high NA throughout the study experienced higher craving overall, and, on days

when NA was higher than usual, craving was also higher. These results suggest high NA may directly contribute to the risk of relapse via increased craving, whereas low PA may contribute to risk of relapse in a subset of people who have persistently low PA, possibly trait-like anhedonia. Gathering real-time data of mood and behavioral outcomes in mental illness and addictions allows for monitoring of symptoms on a time scale that can improve prediction of episodes and facilitate rapid intervention.

Learning Objectives:

- Mobile technologies can be used to monitor symptoms in real-time.
- Understanding development of symptoms in ecologically-valid environment can aid prediction of outcome.

DETECTION OF MOOD STATES FROM ACOUSTIC FEATURES ACQUIRED USING SMARTPHONES

Melvin McInnis, University of Michigan Medical School

Individual Abstract: There is an urgent need to identify biological markers associated with mood states in psychiatric illness and methods (beyond clinical impressions) to monitor and identify changes that can predict illness episodes that require medical or psychological intervention. Clinically, qualitative and quantitative features of speech are associated with mood and mood severity. Family and friends of patients regularly note changes in speech patterns prior to significant mood episodes. This has led to our hypothesis: acoustic features predict and associate with mood states and disease episodes. Participants with rapid cycling bipolar (BP) disorder agreed to use a study smartphone for up to 1 year. Every time a participant engaged in a conversation on the smartphone, his or her speech was recorded, encrypted, and sent to a central server for analyses. A weekly call with a clinician was also recorded while a structured clinical interview (HamD and YMRS) was administered. PRIORI (predicting individual outcomes for rapid intervention) is a program that analyzes acoustics of speech to identify features that associate with mood states. There are two types of calls, assessment calls wherein the participant and clinician are engaged in a telephone based mood assessment (YMRS or HAMD) and personal calls (all other calls). There are 39,950 calls in the database from 47 individuals, with a subset of 1,115 clinical assessment calls. Analyses focused on assessment calls identify acoustic features that associate with mood symptoms, the AUC is 0.69 for predicting the depressive and hypomanic / manic states. We are expanding the data collection to include additional gather native data types (data use related) on the smartphone. The clinical compliance and acceptance with the project is excellent, we expanded the observation time from 6 months to 1 year.

Acquiring acoustic data efficiently using smartphones will allow for ongoing monitoring of mood states and potentially predicting and preventing illness episodes.

Learning Objectives:

- To identity use and advantage of mobile health technology in health care.
- To identify acoustic features in measure of mood disorders.

Literature References:

- Karam ZN, Provost EM, Singh S, et al. Ecologically Valid Long-term Mood Monitoring of Individuals with Bipolar Disorder Using Speech. International Conference on Acoustics, Speech and Signal Processing; 2014; Florence, Italy. p. 4858-62.

- Topol EJ: The patient will see you now: the future of medicine is in your hands. New York, NY, Basic Books; 2015.

DAILY MOOD MONITORING OF SYMPTOMS USING SMARTPHONES IN BIPOLAR DISORDER: FEASIBILITY OF ECOLOGICAL MOMENTARY ASSESSMENT

Erika Saunders, Penn State College of Medicine, Penn State Milton S. Hershey Medical Center

Individual Abstract: Background: Personal device technology has facilitated gathering data in real-time. Ecological Momentary Assessment (EMA) gathers data in the moment about thoughts, feelings, and actions that are occurring. Patients with bipolar disorder (BD) frequently suffer from daily mood symptoms that contribute to disability and relapse. We hypothesized that using smartphones to measure symptoms and related experiences of patients with bipolar disorder (BD) using an EMA protocol would be feasible. A second exploratory objective of this study was to compare core symptoms between BD and healthy control (HC) groups.

Methods: A two-arm, parallel group, observational study was designed to measure completion rates of surveys of symptoms of mood, energy, speed of thought, impulsivity, and social stress in BD (N=10) and HC (N=10) participants. A visual analogue scale was used for rating mood, energy, speed of thoughts, and impulsivity. Social stress was measured using two questions with a Likert scale. Participants were given smartphones programmed to generate surveys automatically twice a day for fourteen days. Participants could also perform self-generated surveys by choice if the auto-generated survey was not completed in the allotted amount of time. Completion rates were compared between BD and HC groups. Scores were averaged for each participant over the 14-day period, and group medians of the survey scores were compared.

Results: Median completion rates of all surveys and of auto-generated surveys did not differ between groups: 95% in BD, 88% in HC (p=0.68); the median completion rate of auto-generated surveys in the BD group was 79% and in the HC group was 71% (p=0.22). Median mood score (p=0.043) and energy score (p=0.007) were significantly lower in the BD than the HC group. Median scores of speed of thoughts (p=0.739), impulsivity (p=0.123) and social stress (p=0.056) did not significantly differ between BD and HC. The BD group had significantly higher range of variability of group median mood (p=0.043), speed of thoughts (p=0.002) and impulsivity (p=0.005) scores over the course of 14 days than HC, while range of variability of energy (p=0.218) and social stress (p=0.123) scores did not differ. Scores were not significantly different between auto-generated and self-generated surveys for BD or HC. This pilot study was conducted for a short time and with a small sample. Conclusions: This study demonstrates feasibility of using EMA with a smartphone to gather data on BD symptoms. Further studies are being conducted to measure these items for a longer time in a larger sample. Measuring symptoms on a daily basis can aid in understanding time course of improvement with treatment, and prediction of future episodes.

Learning Objectives:

- To identify that Ecological Momentary Assessment (EMA) is a technique for measuring symptoms in real time.

- To learn that EMA is feasible for use in bipolar disorder, and captures fluctuations of daily mood symptoms.

Literature References:

- Depp CA, Kim DH, de Dios LV, Wang V, Ceglowski J. A Pilot Study of Mood Ratings Captured by Mobile Phone Versus Paper-and-Pencil Mood Charts in Bipolar Disorder. J Dual Diagn. 2012;8:326-332.
- aan het Rot M, Hogenelst K, Schoevers RA. Mood disorders in everyday life: a systematic review of experience sampling and ecological momentary assessment studies. Clinical psychology review. 2012;32:510-523.

UNDERSTANDING THE RELATIONSHIPS BETWEEN AFFECT AND CRAVING IN EARLY ABSTINENCE: ECOLOGICAL MOMENTARY ASSESSMENT OF PATIENTS IN TREATMENT FOR PRESCRIPTION OPIOID DEPENDENCE

Scott Bunce, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine

Individual Abstract: During the post-withdrawal period from prescription opiates, persistently low positive affect (PA) is likely to contribute to craving – and to the risk of relapse – but has received little attention in clinical research. The current study used ecological momentary assessment (EMA) to examine associations among PA, negative affect (NA), and craving in medically withdrawn patients in residential treatment for prescription opiate-dependence. Participants (n = 73) used programmed smart phones to provide reports of their PA, NA, and craving 4 times per day for an average of 10.47 (SD = 3.80) consecutive days. Between-person (mean level throughout the study) and within-person (day to day variation) associations between PA, NA, and craving were examined using multilevel models. The results indicated that both low PA and high NA were independently associated with increased craving. Controlling for the effects of NA, on days when PA was lower than usual, craving was greater in individuals who reported low mean-levels of PA throughout the study. Controlling for PA, individuals who experienced high mean-levels of NA throughout the study experienced higher craving. At the within-person level, on days when NA was higher than usual, craving was also higher, regardless of participants' mean levels of NA. These results suggest that, whereas high NA may directly contribute to the risk of relapse via increased craving, low PA may make an independent contribution to risk of relapse in a subset of people who have lower average levels of PA. That is, among those who have lower average levels of PA, craving is higher on days they experience lower PA, independent of negative affect, putting them at increased risk for relapse. Given the importance of understanding risk factors for relapse in the early stages of abstinence, further research investigating how and when low PA may create increased risk for relapse is warranted.

Learning Objectives:

- Understanding relationship between persistently low positive affect and craving in opiate dependence.
- Utility of Ecological Momentary Assessment to understand vulnerability to relapse in substance abuse disorders.

Literature References:

- Cheetham A, Allen NB, Yücel M, Lubman DI: The role of affective dysregulation in drug addiction. Clin Psychol Rev 2010; 30:621-634

- McHugh RK, Kaufman JS, Frost KH, Fitzmaurice GM, & Weiss RD: Positive affect and stress reactivity in alcohol-dependent outpatients. J Stud Alcohol Drugs 2013; 74:152–157

PATHWAY TO TREATMENT OF COGNITIVE IMPAIRMENT IN DEPRESSION
Richard Keefe, Duke University Medical Center

Overall Abstract: Cognitive impairment is one of the core features of major depressive disorder, and one of the diagnostic criteria according to DSM and ICD classification systems. Patients with depression report cognitive problems and perform more poorly than healthy controls on cognitive tests. Further, these measures of cognitive impairment are correlated with important aspects of everyday life such as occupational and social functioning. Despite this important unmet need, the pathway to approval of new medicines for cognitive impairment in depression has not been established. Standard antidepressant treatment provides only minor cognitive benefit to patients with depression, and some aspects of cognition may worsen. However, recent studies provide some insight into what aspects of cognition may improve with treatment, and what study designs may best test the capacity of new treatments to provide cognitive benefit. This session will review the importance of cognitive impairment in depression and its relation to key functional outcomes (Dr. Harvey), review the current state of the literature on how standard and new treatments affect cognition (Dr. Fava), and address methodological issues in the assessment of cognition and the design of cognition clinical trials for patients with depression (Dr. Keefe). Finally, Dr. Farchione from FDA will discuss the regulatory perspective on the pathway to approval.
Learning Objectives:
- To understand the importance of cognitive impairment as a treatment target in patients with major depression, and the currently available treatment options.
- To understand the trial design, outcome measures, and regulatory pathway for developing new treatments to improve cognition in patients with major depressions.

COGNITIVE IMPAIRMENT AND DISABILITY IN MAJOR DEPRESSION: WHAT IS THE NATURE OF THE PROBLEM?
Philip Harvey, Miller School of Medicine, University of Miami

Individual Abstract: Cognitive impairment is clearly salient in major depression as highlighted by its inclusion as an element of the diagnostic criteria. Cognitive impairments and disability in major depression have a complex relationship with symptomatic elements of the syndrome. Impairment in everyday functioning in individuals with previous achievements is persistent in at least 25% of patients who achieve clinical remission; remission is attained by less than 50% of patients with current treatments. Patients with treatment resistant depression have substantial cognitive deficits over the course of their illness and they are the group most likely to manifest persistent impairments in everyday functioning. Cognitive deficits have a signature of impairment that appears to be consistent across symptomatic and remitted states. Although the prevalence of residual disability is much less than seen in schizophrenia or bipolar disorder, major depression may be 7-10 times as common as these two conditions, making the problem of residual or persistent disability a larger public health problem than that in these other two conditions. Further, poor work performance in employed patients with major depression is an additional source of morbidity

not as common in schizophrenia. This presentation will review the nature and persistence of cognitive deficits in major depression, as well as the severity and types of everyday disability seen. Also considered will be assessment requirements in domains of cognition and disability, including the content of assessment batteries and the adjustments that need to be made to consider the contributions of symptoms vs. cognition to objective disability in major depression.

Learning Objectives:

- Understand the signature and prevalence of cognitive deficits in major depression.
- Understand the relationship between clinical symptoms, cognitive deficits, and disability in major depression.

Literature References:

- Hammar A, Ardal G. Cognitive functioning in major depression: A summary. Front Hum Neurosci 2009; 3: article 26.
- Reichenberg A, Harvey PD, Bowie CR, et al. Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. Schizophr Bull. 2009;35:1022–9

REVIEW OF TREATMENT STUDIES TO DATE – WHAT DO WE NEED?

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: Cognitive deficits are commonly reported by patients with major depressive disorder. Some cognitive deficits, like mental slowing and concentration difficulties are core components of the diagnostic criteria for Major Depressive Disorder (MDD) and are frequently observed during acute depressive episodes. Some of the cognitive impairments of MDD often improve as the mood symptoms improve, implying a direct relationship between these symptom clusters. It is not clear whether all of these cognitive deficits are part of the core diathesis of MDD or are distinct from the primary disorder and represent treatable independent symptoms. The evidence of a distinct cognitive benefit is often obscured in antidepressant clinical trials of acutely depressed patients as the bulk of the cognitive change is typically driven by the symptomatic changes of the predominant mood symptoms. This presentation will review the relatively modest efficacy of standard antidepressant therapies in the treatment of cognitive impairment in MDD. In fact, any patients whose MDD is in remission following treatment with standard antidepressant therapies experience residual cognitive symptoms that may impair productivity and their quality of life. Residual symptoms of cognitive impairment typically correlate quite poorly with the residual core symptoms of depression. One strategy to differentiate cognitive effects from the mood effects of treatment is to examine changes in cognitive symptoms in depressed patients who do not respond to the tested antidepressant medication, and this strategy has been adopted by a number of investigators. Using this approach, some newer antidepressant therapies have shown beneficial effects in MDD. In addition, this presentation will review commonly used augmentation strategies for the management of residual cognitive symptoms, although the evidence for their efficacy is quite limited.

Learning Objectives:

- Participants will become familiar with the effects of both standard and novel antidepressants on cognitive symptoms in major depressive disorder.
- Participants will also learn about common augmentation strategies used to address residual cognitive symptoms among depressed patients who have responded to antidepressant therapies.

of special interest to clinicians

Literature References:

- Targum SD, Wedel PC, Fava M. Changes in cognitive symptoms after a buspirone-melatonin combination treatment for Major Depressive Disorder. J Psychiatr Res. 2015 Sep;68:392-6
- Rothschild AJ, Raskin J, Wang CN, Marangell LB, Fava M. The relationship between change in apathy and changes in cognition and functional outcomes in currently non-depressed SSRI-treated patients with major depressive disorder. Compr Psychiatry. 2014 Jan;55(1):1-10.

METHODS AND DESIGN OF TRIALS FOR TREATMENT OF COGNITIVE IMPAIRMENT OF MDD

Richard Keefe, Duke University Medical Center

Individual Abstract: While the NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project, with FDA involvement, recommended trial designs and assessment methodologies for the treatment of cognitive impairment in schizophrenia, there has not been a similar process for major depression. Workshops at the Institute of Medicine and the International Society for CNS Clinical Trials and Methodology have initiated discussion on these topics. However, the purpose of those workshops was to stimulate momentum for ongoing dialogue based upon the generation of new data, and significant questions remain in this area of burgeoning interest. This presentation will use current examples from recently published and ongoing clinical trials, as well as the conclusions of the National Academy of Medicine workshop on Neuroscience Trials of the Future, to address key issues for clearing the pathway for drug development targeting cognition in depression: How can this area of work learn from the successes and failures of the MATRICS project? While positive results in schizophrenia cognition trials have been reported, no treatments have received regulatory approval. How should cognitive impairment be defined in depression trials? Many patients perform in the average healthy range on cognitive tests yet complain of cognitive problems even following a return to normal mood. Can issues of heterogeneity and stratification be addressed with biomarkers and neurobiological assays? What designs best address issues of pseudospecificity? Stability of symptoms may be required at baseline for adjunctive medication trials, but monotherapy trials will need to account for symptom improvement that accompanies cognitive change. Are there preferred cognitive and functional assessment domains and instruments? Criteria for these measures need to be established by independent experts. Are there innovative technologies ready for use in multi-site trials? New data on wearables and hand-held cognitive instruments imply that they hold promise, but have not been adequately tested in multisite clinical trial settings.

Learning Objectives:

- To understand the progress in developing designs for clinical trials addressing cognitive impairment in major depression.
- To understand the strengths and weaknesses of the outcome measures for assessing cognitive change in clinical trials for major depression.

Literature References:

- Keefe RSE, McClintock SM, Roth RM, Doraiswamy PM, Tiger S, Madhoo M. Cognitive effects of pharmacotherapy for major depressive disorder: A systemic review. Journal of Clinical Psychiatry, 2014; 75(8): 864-876.

- Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RS. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. Neuropsychopharmacology, 2015; 40(8): 2025-2037.

10:45 a.m. - 12:15 p.m.

Tuesday Mid-Morning Panel Sessions*

STATE VERSUS TRAIT ANHEDONIA: A NEUROBIOLOGICAL LINK BETWEEN DEPRESSION, ADHD AND SUBSTANCE ABUSE

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Overall Abstract: Due to high prevalence rates, early onset, persistence, and impairment, mental disorders are a major contributor to total disease burden. Despite advances in research and diagnostic tools, there remain no objective biomarkers to guide diagnosis and treatment. While there are defined diagnostic criteria, treatment guidelines and available effective antidepressants, significantly fewer patients than expected diagnosed with Major Depressive Disorder (MDD) achieve remission, resulting in residual symptoms, functional impairment and higher rates of suicide. Lack of remission may be explained by the high prevalence of comorbid disorders, heterogeneity of symptomology and complex etiologies involving genetic and non-genetic risk factors.

An accumulation of evidence has demonstrated that cognitive dysfunction including impairment in working memory, executive function, attention, ideational fluency, visuo-spatial function, and learning, is strongly associated with impaired life functioning despite adequate dose and duration of pharmacological treatment.

Executive dysfunction, suggesting prefrontal cortex dysfunction, is the hallmark symptom of Attention-Deficit/Hyperactivity Disorder (ADHD). Although ADHD has gained acceptance as a valid diagnosis in the adult population, many clinicians fail to adequately screen patients for ADHD during psychiatric assessment despite the evidence that adolescents with a history of ADHD are significantly more likely to develop MDD, an anxiety disorder and/or substance abuse. Recent research has suggested a neurobiological link between MDD, ADHD and substance abuse that may predict a poor outcome when treated with traditional antidepressants.

This panel will discuss the epidemiology of comorbid disorders, clinical and diagnostic challenges in achieving full remission, and present neurobiological links between depression, ADHD and substance abuse with an emphasis on cognitive functioning. The use of neuropsychological and behavioral markers as predictors of treatment outcome and appropriate and effective treatment strategies including the use of stimulants and medical marijuana will be addressed. This panel is designed for clinicians interested in early detection and optimal treatment of patient with MDD and comorbid conditions.

Learning Objectives:

At the end of the session participants will:

- Understand the prevalence and impact of residual symptoms associated with MDD and be able to apply a novel approach to differentiating residual cognitive symptoms from comorbid disorders.
- Identify a neurobiological link between MDD, ADHD and substance abuse that may predict treatment outcome in order to guide treatment selection including the appropriate use of stimulants and medical marijuana.

UNDERSTANDING THE BIOLOGICAL BASIS OF CO-OCCURRING DEPRESSION AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Irvin Epstein, University of Toronto

Individual Abstract: Over the past decade, much research has focused on mapping neural circuits and understanding mechanisms of neurochemical action, as well as the identification of specific genetic loci in order to increase the understanding of neurobiological dysfunction in both psychiatric and neurodevelopment illnesses. Despite these advances, there remains a significant unmet need for effective and comprehensive diagnostic techniques and treatments. At present, psychiatric illness represents 13% of the global burden of disease, and is the leading cause of disability in the United States. Moreover, suicide related to depression and other psychiatric conditions is the 10th leading cause of death, with more than 40,000 cases reported annually in the United States alone.

Depression is a psychiatric disorder with complex and variable genetic and non-genetic risk factors that interact with and are altered by one's life experiences. Genetic studies have identified altered neural pathways, which affect emotional, cognitive, introception and self-awareness that provide a new conceptual model of the evolution of depressive symptoms. Moreover, recent research has demonstrated that children diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) have profound and consistent delays in cortical neuronal network refinement and maturation, specifically in the prefrontal cortex, which accounts for cognitive and attentional impairments.

While the diagnostic criteria for Major Depressive Disorder (MDD) is well defined, there continues to be a high percentage of individuals with MDD that experience residual symptoms, despite adequate dose and duration of pharmacological treatment. The presence of subclinical and/or atypical depressive symptoms presents clinical challenges, which result in delays in both detection and the introduction of targeted treatment, particularly in the presence of comorbid disorders. Current literature suggests that the potential for full remission in MDD after adequate treatment is in the order of 30-40% and a majority of patients experience, residual symptoms, specifically cognitive impairment, which is not often reported by the patient nor assessed by the clinician.

Thus the need to accurately differentiate between residual symptoms of MDD and the presence of comorbid or premorbid cognitive symptoms of ADHD is critical to treatment selection and the goal of improved patient outcomes.

This presentation will focus on the prevalence of MDD and the effect of comorbid ADHD, as well as recent research that has demonstrated potential vulnerabilities and associated risk factors that may play a role in the development of treatment-resistant depression. In addition, the neurobiological determinants and genetic factors associated with the development of comorbid ADHD and substance abuse within the depressed population will be discussed. As

well, evidence of unique biological selectivity and rationale for behavioral and emotional symptomology of MDD will be addressed with a focus on the potential for developing cognitive and attentional dysfunction.

Learning Objectives:

- To understand the impact and prevalence of cognitive impairment as well as other related symptoms on the presentation of comorbidity of MDD and ADHD.
- To understand the role of translational research integrating evidence from the lab and neuroimaging into improvements in the diagnosis and management of these co-occurring conditions.

Literature References:

- de Sousa RT, Zanetti MV, Brunoni AR, Machado-Vieira R. Challenging Treatment-Resistant Major Depressive Disorder: A Roadmap for Improved Therapeutics. Curr Neuropharmacol. 2015;13(5):616-35.
- Onnink AM, Zwiers MP, Hoogman M, Mostert JC, Kan CC, Buitelaar J, Franke B. Brain alterations in adult ADHD: effects of gender, treatment and comorbid depression. Eur Neuropsychopharmacol. 2014 Mar;24(3):397-409.

THE NEUROBIOLOGY OF COGNITIVE DYSFUNCTION AND ANHEDONIA: A COMMON LINK BETWEEN PSYCHIATRIC DISORDERS AND THE EFFECTS ON TREATMENT SELECTION

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Individual Abstract: Cognitive impairment is often exhibited in patients presenting with depressive disorders and remains in approximately 30-50% of patients diagnosed with Major Depressive Disorder (MDD) despite adequate duration and dose of traditional pharmacotherapy. Cognitive impairment, which impacts motivation, energy, memory, planning and task initiation, psychomotor speed, attention and facial recognition, results in social, occupational and academic impairment as well as higher rates of suicidal ideation and attempts. Moreover, cognitive dysfunction is exacerbated by common comorbidities such as Attention-Deficit/Hyperactivity Disorder (ADHD) and substance abuse, which presents diagnostic and treatment challenges, as well as a reduced quality of life and shorter life expectancy for patients.

In the absence of objective biomarkers to determine precise etiology and guide treatment selection, an understanding of the neurobiology and associated symptomatic presentation is essential. While the catecholaminergic systems have long been accepted as critical to the modulation of goal-directed behavior and executive function, recent evidence has demonstrated that the endocannabinoid system is associated with prefrontal activity including executive dysfunction present in many psychiatric conditions including ADHD, substance use and MDD.

Moreover, the prefrontal cortex, caudate, cerebellum, and decreased dopamine receptors have been implicated in the etiology of cognitive impairment in both MDD and ADHD. This shared etiopathology and specific behavioral markers, such as anhedonia may provide insight into the appropriate use of pharmacological agents to improve patient outcomes in a subset of patients. In this section, the neuroanatomy and neurobiology of cognitive dysfunction will be reviewed with an emphasis on recent data from neuropsychology, genetics and imaging that suggest a common link between these disorders in a subset of patients. Implications for

clinical and diagnostic techniques will be discussed as well as the use of pharmacological agents including stimulants and medical marijuana.

Learning Objectives:

- To understand the role of the prefrontal cortex, caudate, cerebellum, in relations to catecholaminergic inactivity as implicated in the etiology of depleted motivation, energy cognitive impairment in both MDD.
- To understand the association between mood symptoms, dysthymia and ADHD in relation to prefrontal activity with a focus on the interaction between catecholamines and the glutamate, GABA and the endocannabinoid systems.

Literature References:

- Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. J Am Acad Child Adolesc Psychiatry 2012; 51(4):356-67.
- Bossong MG, van Hell HH, Jager G, Kahn RS, Ramsey NF, Jansma JM. The endocannabinoid system and emotional processing: a pharmacological fMRI study with Δ9-tetrahydrocannabinol. Eur Neuropsychopharmacol 2013;23(12):1687-97.

ANHEDONIA: A PREDICTOR OF COGNITIVE DYSFUNCTION, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND TREATMENT OUTCOME IN A SUBSET OF DEPRESSED PATIENTS

Tia Sternat, START Clinic for Mood & Anxiety Disorders

Individual Abstract: An increasing emphasis has been placed on the prevalence and severity of residual symptoms, specifically cognitive impairment and anhedonia, in patients diagnosed with Major Depressive Disorder (MDD) in an effort to improve treatment outcomes and quality of life. The absence of established biomarkers presents diagnostic challenges in the clinical setting, specifically in patients presenting with MDD and comorbid disorders including Attention-Deficit/Hyperactive Disorder (ADHD). Recent research suggests a neurobiological link between MDD and ADHD in a subset of patients, which may predict treatment outcome when treated with traditional antidepressants. Moreover, there is an accumulation of evidence that suggests that the presence of anhedonia may predict treatment outcome in depressed patients when treated with selective serotonin reuptake inhibitors. ADHD is among the most common neurocognitive disorders observed in patients with mood and anxiety disorders. While ADHD has been accepted as a valid adult diagnosis, clinicians are faced with obstacles in early diagnosis and accurate detection, which is further complicated in the presence of substance use. Given the high prevalence rate of comorbid ADHD with depression, differentiating between residual symptoms and premorbid cognitive impairment is essential for selecting appropriate treatment and improving treatment outcomes.

This session will review the epidemiology of MDD with a focus on cognitive dysfunction and anhedonia as well as discuss the implications of state versus trait anhedonia on treatment outcome. Predictive risk factors and behavioral features will be reviewed in order to determine potential clinical and diagnostic tools to improve accurate detection of ADHD and identify anhedonic features that may be predictive of treatment-resistance. A case study will be presented to highlight the use of neurobiological markers to differentiate and improve

treatment outcomes in a subgroup of depressed patients at risk for developing treatment resistant depression and presenting with residual cognitive symptoms.

Learning Objectives:

- To describe a common link between the neurobiology of depression and ADHD as a risk factor for development of treatment-resistance in a subset of patients.
- To identify predictive factors and behavioral markers associated with anhedonia as a method to subtype depressive disorders in order to optimize treatment outcome.

Literature References:

- McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor-treatment resistant depression. J Am Acad Child Adolesc Psychiatry 2012;51(4):404-11.
- Meinzer MC, Lewinsohn PM, Pettit JW, Seeley JR, Gau JM, Chronis-Tuscano A et al. Attention deficit-hyperactivity disorder in adolescence predicts onset of major depressive disorder through early adulthood. Depress Anxiety 2013;30(6):546–53.

UNRAVELING THE COMPLEXITIES OF PSYCHOTROPIC PRESCRIBING DURING PREGNANCY*

Lee Cohen, Massachusetts General Hospital

Overall Abstract: The last two decades have brought numerous studies describing a spectrum of issues in reproductive mental health including: 1) course of psychiatric disorder during pregnancy, 2) extensive data regarding risks of fetal exposure to medications used to treat psychiatric disorders, and 3) obstetrical and neonatal outcomes associated with untreated psychiatric disorder. The clinical calculus including the weighing of factors which ultimately allows for thoughtful decision-making regarding women treated with psychiatric medications is increasingly complex and without an absolutely quantified formula or road map. This panel will include presentations which address critical elements of the current state-of-knowledge regarding risks of fetal exposure to psychiatric medications used to treat psychiatric disorders during pregnancy. In the first presentation, Dr. Lee Cohen will describe data regarding course of bipolar disorder during pregnancy and will then review available reproductive safety data on mood stabilizers including second generation antipsychotics. Data regarding outcomes following fetal exposure to atypical antipsychotics will derive largely from the new National Pregnancy Registry for Atypical Antipsychotics at Massachusetts General Hospital. Dr. Marlene Freeman will provide an overview of available data on associated risks of antidepressant use during pregnancy with a focus on the extent to which data derived from large administrative databases help or complicate our ability to quantify risk associated with antidepressant use during pregnancy. This presentation will also include a description of the new FDA pregnancy labeling rules which have replaced the previous category label system. In the third presentation of this panel, Dr. Samantha Meltzer-Brody will review the available information regarding impact of untreated psychiatric disorder on fetal well-being as well as obstetrical and neonatal outcomes described in the literature across samples of women with documented psychiatric disorder during pregnancy. The translational underpinning of adverse outcomes in the setting of untreated psychiatric disorder during pregnancy will be a cornerstone of this presentation. Lastly, Dr. Alan Gelenberg will serve as discussant for this panel and will integrate the key elements of each presentation, providing the audience with a conceptual framework for understanding the state of the science regarding the relative risks

of treating psychiatric disorder during pregnancy and a critical road map for navigating the treatment of this population when there are no "perfect" decisions.

Learning Objectives:

- To address critical elements of the current state-of-knowledge regarding risks of fetal exposure to psychiatric medications used to treat psychiatric disorders during pregnancy.
- To provide a conceptual framework for understanding the state of the science regarding relative risks of both treated and untreated psychiatric disorder during pregnancy.

SECOND GENERATION ANTIPSYCHOTICS IN REPRODUCTIVE AGE WOMEN: CURRENT RESULTS FROM THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS

Lee Cohen, Massachusetts General Hospital

Individual Abstract: Background: Despite widespread use of atypical antipsychotics in women of childbearing potential, reproductive safety data across these medicines are sparse. The National Pregnancy Registry for Atypical Antipsychotics was established to address this knowledge gap.

Methods: Eligible enrollees include pregnant women between 18 and 45 years of age. The exposed group is comprised of women who have taken atypical antipsychotics during pregnancy; the comparison group is comprised of women with psychiatric illness who have not taken this class of medication during pregnancy. Three phone interviews are conducted: 1) baseline 2) 7 months gestation, and 3) 3 months postpartum. Obstetric, labor and delivery, and pediatric medical records are obtained. Potential malformations are identified and relevant records are sent to a dysmorphologist blinded to drug exposure for adjudication.

Results: As of October 2015, total enrollment in the Registry was 583 women. A total of 385 women have completed the study and were eligible for inclusion in the analysis. Of 263 live births with first trimester exposure, three (N=3) malformations were confirmed. Of the 122 control group live births, one (N=1) malformation was confirmed. The absolute risk of malformations was 1.14% among exposed infants and 0.8% among unexposed infants. The odds ratio for malformations was 1.40 (0.14, 13.56) comparing exposed to unexposed infants, not reaching statistical significance.

Discussion: The Registry offers a systematic way to collect prospective reproductive safety information which informs the care of women who may use atypical antipsychotics to sustain emotional well-being. These preliminary data suggest that it is unlikely that second generation antipsychotics are major teratogens; greater numbers of enrolled and control subjects will refine the risk estimate for major malformations and other relevant obstetric and neonatal outcomes.

Learning Objectives:

- To review available reproductive safety data on mood stabilizers including second generation antipsychotics, with specific emphasis on current data from the National Pregnancy Registry for Atypical Antipsychotics.
- To describe preliminary data from the National Pregnancy Registry for Atypical Antipsychotics regarding obstetrical outcomes, including weight gain, following fetal exposure to atypical antipsychotics.

of special interest to clinicians

Literature References:

- Cohen LS, Viguera AC, McInerny KA, et al: Reproductive Safety of Second-Generation Antipsychotics: Current Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. Am J Psychiatry 2015; 0(0):appi.ajp.2015.15040506.
- Cohen LS, Viguera AC, McInerney KA, et al: Establishment of the National Pregnancy Registry for Atypical Antipsychotics. J Clin Psychiatry 2015; 76:986–989.
- Coughlin CG, Blackwell KA, Bartley C, et al: Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. Obstet Gynecol. 2015 May;125(5):1224-35.

BASELINE BMI AND GESTATIONAL WEIGHT GAIN IN WOMEN WITH PSYCHIATRIC ILLNESS: IMPACT OF PSYCHOTROPIC USE AND CLINICAL IMPLICATIONS

Marlene Freeman, Massachusetts General Hospital Simches Research Building

Individual Abstract: Directly or indirectly, obesity has a major effect on the morbidity and mortality associated with pregnancy. The U.S. pregnancy-related mortality rates have been steadily rising, and pregnant women have been increasingly diagnosed with obesity related illnesses, such as hypertension, diabetes, and heart disease [1]. Having a psychiatric diagnosis of a mood or psychotic disorder increases the risk obesity, and many psychotropics have associated weight gain as part of their adverse event profiles. Therefore, the prevalence of overweight/obesity at the onset of pregnancy and rates of gestational weight gain are clinically important variables pertaining to women with psychiatric disorders. These topics will be discussed, along with original data from the National Pregnancy Registry for Atypical Antipsychotics. In this prospective registry, women are closely followed for pregnancy and neonatal outcomes, while psychotropic use and weight are carefully tracked. Women on atypical antipsychotic medications started pregnancy at higher body mass indexes (BMI) than controls with psychiatric diagnoses, although weight gain during pregnancy is similar between groups. Both groups also gained more weight during pregnancy than is recommended by Institute of Medicine guidelines for weight gain during pregnancy, a concern that pertained to women who started pregnancy at normal weight (BMI 18.5-24.9), overweight (25.0-29.9), or obese (>29.9).

Learning Objectives:

- To discuss the clinical implications of overweight/obesity as a risk factor for obstetric morbidity.
- To discuss the specific implications of weight-related pregnancy risk for women with psychiatric disorders and the relevant considerations of psychotropic use before and during pregnancy.

Literature References:

- Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Rev. 2015;16(8):621-38.
- CDC ref: http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html

OBSTETRICAL, PREGNANCY, AND SOCIOECONOMIC PREDICTORS FOR POSTPARTUM PSYCHIATRIC DISORDERS

of special interest to clinicians

Samantha Meltzer-Brody, University of North Carolina at Chapel Hill

Individual Abstract: Background: Women with untreated psychiatric disorders during pregnancy may have an increased risk of obstetrical complications and adverse neonatal outcomes. In particular, maternal psychiatric and medical complications occurring during pregnancy and/or childbirth have been linked to postpartum psychiatric illness. Methods: Comprehensive review of the literature was performed. In addition, a population-based cohort study using the Danish registers was conducted in 435,034 primiparous women with a singleton delivery between 1995 and 2012 and no previous psychiatric history. The main outcome was first-onset postpartum psychiatric episodes. Incidence rate ratios were calculated for any psychiatric contact in 90-day intervals for the first year postpartum. Results: A literature review demonstrated that untreated psychiatric disorders during pregnancy are associated with increased risk of adverse obstetrical and neonatal outcomes. Danish register data showed that medical complications during pregnancy increased the risk of postpartum psychiatric disorders. Women diagnosed with postpartum depression had increased risk of hyperemesis gravidarum, (RR=2.69; 95% CI: 1.93-3.73), gestational hypertension (IRR=1.84; 95% CI: 1.33-2.55), preeclampsia (IRR=1.45; 95% CI: 1.14-1.85), and C-section (IRR=1.32; 95% CI: 1.13-1.53). For postpartum acute stress/PTSD, hyperemesis gravidarum (IRR=1.75; 95% CI: 1.26-2.41), preterm birth (IRR=1.51; 95% CI: 1.30-1.75), gestational diabetes (IRR=1.42; 95% CI: 1.02-1.97), and C-section (IRR=1.36; 95% CI: 1.20-1.55) were associated with increased risk.

Conclusions: Untreated psychiatric and medical complications during pregnancy can increase the risk for adverse obstetrical, neonatal and maternal psychiatric outcomes. The underlying pathophysiology that leads to increased risk is important to elucidate in order to improve outcomes for both mother and child.

Learning Objectives:

- Understand the impact of untreated psychiatric disorders in pregnancy on obstetrical and neonatal outcomes.
- Discuss the underlying mechanisms whereby untreated psychiatric and medical complications during pregnancy can increase the risk for adverse obstetrical and postpartum psychiatric outcomes.

Literature References:

- Gentile S. Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. Neuroscience. 2015 Sep 4. [Epub ahead of print].
- Blom EA, Jansen PW, Verhulst FC, et al: Perinatal complications increase the risk of postpartum depression. The Generation R Study. BJOG 2010;117, 1390-8.

FRONTIERS OF PHARMACOTHERAPY FOR AUTISM SPECTRUM DISORDERS*

Stephen Zukin, Johns Hopkins University School of Medicine

Overall Abstract: Impairment of social communication and interaction and restricted, repetitive patterns of behavior and interests are the core deficits in autism spectrum disorder (ASD). Development of efficacious pharmacotherapies targeting these faces daunting challenges at the clinical trial stage, including genetic and phenotypic heterogeneity, subject

stratification issues, and outcome measure selection in the absence of validated measures with proven sensitivity to change in a clinical trial setting.
An important strategy has been to target circuitry related to social communication and interaction, based upon translational and biomarker research findings. This panel will present emerging findings from studies involving three distinct molecular targets. The discussant will place these approaches in the context of the growing understanding of genetics and pathophysiology of ASD.

Learning Objectives:

- Understand the challenges and opportunities of ASD clinical trials.
- Understand the potential of distinct molecular targets to address core deficits of ASD.

ENDPOINT SELECTION AND STRATIFICATION VARIABLES FOR CLINICAL TRIALS IN AUTISM: LESSONS FROM THE ARBACLOFEN PROGRAM

Paul Wang, Autism Speaks

Individual Abstract: While significant advances have been made in the genetics and neurobiology of autism, drug development targeting the core symptoms of autism remains an unfulfilled promise. No regulatory precedents exist for approval of such an indication. Arbaclofen is a GABA-B receptor agonist, and is an enantiomer of racemic baclofen, which is labeled in the USA for the treatment of spasticity associated with multiple sclerosis. Racemic baclofen also is widely prescribed to children for spasticity associated with cerebral palsy, and its pediatric safety profile is thus well understood. The potential utility of arbaclofen in autism is grounded in the imbalance of excitatory vs. inhibitory neurotransmission that characterizes autism, both in animal models and in MRS studies of patients. Preclinical studies show that arbaclofen rescues both behavioral and neuropathological phenotypes in animal models of fragile X syndrome, which is the most common genetic etiology of autism, and also shows benefits in other animal models.

The clinical development program for arbaclofen is among the largest and broadest industry-sponsored efforts in this space. Over 500 subjects, across the pediatric and adult age ranges, were enrolled in Phase 2 and 3 studies targeting core social symptoms and social-communicative function in autism and in fragile X syndrome. In this session, we will present the design and results of the clinical studies of arbaclofen. The presentation will focus on endpoint selection and endpoint performance, including discussions with regulatory authorities on outcome measures, observations on measurement sensitivity and placebo response, stratification variables, and the utility of biomarker assessments.

Learning Objectives:

- Explain the utility and shortcomings of available outcome assessments for autism.
- Identify potentially important stratification variables for efficacy assessment in autism.

Literature References:

- Berry-Kravis E, Hessl D, Rathmell B et al. Effects of STX209 (Arbaclofen) on Neurobehavioral Function in Children and Adults with Fragile X Syndrome: A Randomized, Controlled, Phase 2 Trial. Science Translational Medicine. 2012;4(152):152ra127-152ra127. doi:10.1126/scitranslmed.3004214.

- Anagnostou E, Jones N, Huerta M et al. Measuring social communication behaviors as a treatment endpoint in individuals with autism spectrum disorder. Autism. 2014;19(5):622-636. doi:10.1177/1362361314542955.

DESIGNING CLINICAL TRIALS TO ENHANCE FUNCTIONING IN DEVELOPMENTAL DISORDERS: MOVING FROM SINGLE DOSE STUDIES OF OXYTOCIN TO SUSTAINED TREATMENT TRIAL IN AUTISM

Linmarie Sikich, Duke University Medical Center

Individual Abstract: Oxytocin has been recognized for its impact upon social affiliation for decades. However, its potential use as a treatment for autism only moved forward after a series of single-dose studies of intranasal oxytocin demonstrated improvements on lab-based assessments of social cognition in individuals with autism, typical development and other psychiatric conditions. The pressure to explore intranasal oxytocin as a treatment for autism was further spurred by functional imaging studies demonstrating changes in brain activation patterns during socially relevant tasks after intranasal oxytocin as compared to placebo. However initial studies of sustained oxytocin treatment in ASD have had inconsistent results. There are multiple factors that may underlie these largely disappointing results. First, the single dose studies did not explore a range of doses and did not examine the duration of observed effects. In addition, there has been minimal research on potential correlations between peripheral or brain concentrations of oxytocin and observed responses. Also, the duration of these trials (1-12 weeks) may be too short to observe the development of new skills or behaviors in contrast to assessing changes in symptoms. Further, little attention has been paid to how heterogeneity in age, pathophysiological mechanisms of illness, and current social functioning might influence response to a specific intervention. The large, NIH-funded Study of Oxytocin in Autism to enhance Reciprocal Social Behaviors - SOARS-B was designed to try to address some of these concerns.

Learning Objectives:

- Explain two ways in which knowledge of pharmacokinetics could influence the design and outcome of a clinical trial.
- Describe two issues related to the duration of a clinical trial focused on facilitating development of new functional abilities.

Literature References:

- Insel TR: Translating oxytocin neuroscience to the clinic: a National Institute of Mental Health perspective. Biological Psychiatry 2016; 79(3):153-154.
- Dawson G, Rogers S, Munson J, et al.: Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. Pediatrics 2010; 125(1): e17-23.

OPPORTUNITIES AND CHALLENGES IN AUTISM DRUG DEVELOPMENT: THE INDUSTRY PERSPECTIVE

Federico Bolognani, Roche Innovation Center Basel / F. Hoffmann-La Roche, Ltd.

Individual Abstract: During the last decade, basic research on Autism Spectrum Disorder (ASD), from genetics to brain imaging, has generated a broad wealth of knowledge in the

physiopathology of ASD. These findings are providing new opportunities for developing targeted drugs to treat core aspects of ASD, such as social and communication deficits. The big challenge for the pharmaceutical industry involves the translation of these early findings into registrational trials that will allow these new therapies to reach the ASD population. Since there are no FDA approved drugs to treat core deficits in ASD and only a few multicenter studies have been conducted, there is a lack of consensus and no precedence for: 1) regulatory paths for marketing approval; 2) accepted endpoints for health authorities, payers and the community; 3) clear understanding of best study designs; and 4) how to reach the paediatric ASD population without delays.

As such, the industry is facing the challenge of developing new drugs concomitantly with building the regulatory and scientific path to translate and demonstrate the effect of investigational drugs. In this context, pre-competitive collaborations between the industry, the academia, health authorities, advocacy groups and private foundations are critical for early successes in the development of drugs to improve the life of patients with ASD and their families.

Learning Objectives:

- Perspective of the pharmaceutical industry on ASD drug development.
- Importance of pre-competitive collaborations.

Literature References:

- Anagnostou E, Jones N, Huerta M, Halladay AK, Wang P, Scahill L, Horrigan JP, Kasari C, Lord C, Choi D, Sullivan K, Dawson G. Measuring social communication behaviors as a treatment endpoint in individuals with autism spectrum disorder. Autism. 2015 Jul;19(5):622-36.
- Jeste SS, Geschwind DH. Clinical trials for neurodevelopmental disorders: At a therapeutic frontier. Sci Transl Med. 2016 Jan 13;8(321):321fs1.

BIOMARKER BASED CLINICAL TRIALS IN DRUG DEVELOPMENT

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: Despite the current crisis in medication development for major psychiatric disorders, research activity in pharmaceutical and biotechnology industries has been decreasing. Simultaneously, there has been a growing recognition that the vast majority of available medications while widely prescribed do not substantially reduce morbidity or mortality from these devastating illnesses.

These problems have crystalized the need for a focus on evaluating and establishing efficacy for novel interventions that can show evidence of mechanism and target engagement in clinical populations. NIMH has also shifted from large clinical trials that promise an incremental improvement to an experimental medicine approach. This approach understandably depends on human studies and not on animal studies. Clinical studies for the experimental medicine approach could as a result be small but would include pre-specified biomarkers and neurobehavioral outcomes.

This panel will include a discussion on design and analyses considerations for such trials (Bill Potter) and the biosignature development of placebo and active treatment response (EMBARC trial). The panel will focus on specific topics that illustrate examples of validated biomarkers to make the case that biomarker based studies that evaluate a priori defined biomarkers such as resting state-connectivity, reward processing, emotional processing, EEG

or blood based markers can be used to successfully design clinical trials. Dr. Mayberg will discuss testing imaging biomarkers for treatment stratification in Depression, Dr. Andrew Krystal will discuss use of anhedonia as a clinical marker on imaging parameters and Dr. Giacomo Salvadore will discuss the use of evidence of inflammatory markers in the design of RCTs.

Learning Objectives:

- Discuss use of specific biomarkers to test efficacy of related interventions.
- Discuss patient selection related to biomarker based RCTs.

TOWARDS IMAGING BIOMARKERS FOR TREATMENT SELECTION IN MAJOR DEPRESSIVE DISORDER

Helen Mayberg, Emory University School of Medicine

Individual Abstract: Though antidepressant treatments are highly effective in some individuals, there is no reliable method to match depressed patients to their best option. Needed is a clinically viable algorithm that selects the best treatment and avoids ineffective ones, while also identifying patients that require alternatives to standard first-line interventions. Towards this goal, this presentation presents findings from a series of resting state positron emission tomography and magnetic resonance imaging studies examining baseline patterns predictive of differential response to different treatments. FDG PET and complementary resting-state fMRI imaging biosignatures have been defined that stratify patients into two distinct subtypes predictive of likely remission to escitalopram or cognitive behavioral therapy as well as identify those patients who will fail combined treatment. Parallel studies in known treatment resistant patients further identify additional functional imaging patterns providing additional evidence of biologically distinct depression subtypes with relevance to treatment selection and optimization at all stages of illness. Analytic strategies that consider comparisons of fMRI and PET as well as non-imaging surrogates will be necessary to determine the most accurate and accessible method for clinical use in individual patients.

Learning Objectives:

- To understand available imaging options for treatment selection biomarker development.
- To appreciate analytic strategies used to determine accuracy of identified 'biomarkers.'

Literature References:

- McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR, Craddock RC, Mayberg HS: Toward a Neuroimaging Treatment Selection Biomarker for Major Depressive Disorder. JAMA Psychiatry 2013; 70:821-9.
- Dunlop BW, Mayberg HS: Neuroimaging-based biomarkers for treatment selection in major depressive disorder. Dialogues Clin Neurosci 2014; 16: 479-90.

RATIONALE FOR THE DESIGN OF THE NIMH FAST-MAS BIOMARKER-BASED CLINICAL TRIAL

Andrew Krystal, Duke Clinical Research Institute and Department of Psychiatry and Behavioral Sciences Duke University School of Medicine

Individual Abstract: Despite recent breakthroughs in basic science and in understanding aspects of the pathophysiology of neuropsychiatric disorders, there is a dearth of new therapeutics in the CNS discovery pipeline and FDA approvals of CNS drugs with novel mechanisms are nearly non-existent. Flaws in the traditional methodology of early phase clinical trials (Phase 1 and Phase 2a) have been identified as among the most important impediments to the successful development of CNS drugs. One of the key flaws in the traditional methodology has been the use of high-variability outcome measures which cause reasonably-sized phase 2 trials to be under-powered and unreliable as a basis for making decisions regarding Phase 3.
Here we present an alternative approach which employs biomarkers to assess outcome. This approach is being implemented in the NIMH supported program: New Experimental Medicine Studies: Fast-Fail Trials in Mood and Anxiety Spectrum Disorders (FAST-MAS). We outline the key rationale for this approach and for critical aspects of the study design. This includes choosing the biomarker to employ, deciding whether to use a biomarker as part of the subject inclusion criteria, standardizing biomarker-related methodology across sites, and interpretation of findings. These considerations will be illustrated in detail through their application in an ongoing study which is intended to determine whether engaging kappa opioid receptors with an antagonist molecule will increase ventral striatal activation in anticipation of reward.

Learning Objectives:

- Understand the problems with early phase trials that speak to the need for biomarker-based clinical trials.
- Appreciate the methodologic challenges inherent in designing a biomarker-based clinical trial.

Literature References:

- Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010 Mar;9(3):203-14.
- Insel TR, Scolnick EM. Cure therapeutics and strategic prevention: raising the bar for mental health research. Mol Psychiatry. 2006 Jan;11(1):11-7.

INTERLEUKIN-6 INHIBITION AS A POTENTIAL TREATMENT STRATEGY FOR DEPRESSION: A PROOF OF CONCEPT STUDY WITH SIRUKUMAB IN DEPRESSED PATIENTS WITH SUBOPTIMAL RESPONSE TO ANTIDEPRESSANTS AND ELEVATED PERIPHERAL INFLAMMATORY MARKERS

Giacomo Salvadore, Janssen Pharmaceuticals

Individual Abstract: Accumulating evidence suggests that patients with major depressive disorder display abnormalities of peripheral inflammatory markers, and that those abnormalities might be more pronounced in subjects who do not respond to conventional monoaminergic antidepressants. Among the peripheral markers of inflammation associated with depression, Interleukin-6 (IL-6) emerges as one of the most consistently elevated biomarkers as indicated by meta-analyses. Furthermore, post-hoc analyses of trials with monoclonal antibodies against IL-6 in non-psychiatric inflammatory conditions show a potential beneficial effect against the core symptoms of depression, which appears at least partially independent from the clinical benefits in the primary medical condition. Preclinical

data from the social defeat stress depression model also suggest that IL-6 has a fundamental role in mediating the phenotype susceptible to depressive-like behaviors and that administration of an anti-IL-6 monoclonal antibody prevents development of the depression-like phenotype in this model. Taken together the existing data support a potential role of IL-6 inhibition as a target for novel antidepressant approaches.
Sirukumab is a human anti-IL-6 monoclonal antibody currently in development for rheumatoid arthritis and other associated conditions which showed an antidepressant signal in a study in RA. An on-going study sponsored by Janssen Research & Development is testing the hypothesis that IL-6 inhibition through sirukumab subcutaneous administration is associated with antidepressant effects in subjects with Major Depressive Disorder with suboptimal response to current antidepressant treatment who exhibit elevated levels of C-Reactive Protein (CRP). This trial represents one of the first examples where a stratified medicine approach is applied to an industry-sponsored trial in psychiatry. This presentation will discuss the rationale behind the choice of CRP as an enrichment marker, as well as preliminary data from the CRP screening experience within this trial.

Learning Objectives:

- To discuss the rationale for inhibition of the proinflammatory cytokine, IL-6, as a potential antidepressant strategy.
- To discuss the challenges and the potential solutions for a stratified medicine approach in depression drug development through the example of the on-going proof of concept trial with the anti-IL-6 antibody sirukumab.

Literature References:

- Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffe DJ, Bregman D, Rebusi N, Heshmati M, Aleyasin H, Warren BL, Lebonté B, Horn S, Lapidus KA, Stelzhammer V, Wong EHF, Bahn S, Krishnan V, Bolaños-Guzman CA, Murrough JW, Merad M, Russo SJ: Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc Natl Acad Sci U S A. 2014;111:16136-41.
- Fonseka TM, McIntyre RS, Soczynska JK, Kennedy SH: Novel investigational drugs targeting IL-6 signaling for the treatment of depression. Expert Opin Investig Drugs 2015;24:459-75.

2:00 p.m. - 4:00 p.m.

Pharmaceutical Pipelines

CENTANAFADINE SR (CTN-SR) DEMONSTRATES BRAIN OCCUPANCY AT NOREPINEPHRINE TRANSPORTER (NET), SEROTONIN TRANSPORTER (SERT) AND DOPAMINE TRANSPORTER (DAT) USING SINGLE PHOTON EMISSION TOMOGRAPHY (SPECT) IN HEALTHY VOLUNTEERS (HVS)

Danna Jennings[2], Olivier Barret[3], Gary Wisniewski[3], Kenneth Marek[3], Anthony McKinney[1], Catherine O'Brien[4], Gary Maier[5], Connie Reininger[6], Gilles Tamagnan[3], David Alagille[3], John Seibyl[3]*

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Abstract: Background: Central modulation of serotonin, norepinephrine and dopamine appears to underlie the efficacy for a variety of psychiatric therapeutics. CTN-SR is an investigational monoamine transport inhibitor in development for treatment of attention deficit hyperactivity disorder (ADHD) and its comorbidities, such as mood and anxiety disorders. The purpose of this study was to determine brain occupancy of CTN-SR at NET, SERT and DAT in HVs. In addition, occupancy studies utilizing methylphenidate (MPH) and atomoxetine (ATX) as agents with expected DAT and NET occupancy, respectively, were performed fusing the same methodology for comparison.
Methods: [123I] INER was the radiotracer used to measure NET, while [123I]β-CIT was the radiotracer used for imaging SERT and DAT. Oral dosing with CTN-SR, MPH-LA and ATX was titrated for post dose imaging at steady state. For NET target occupancy studies, HVs received CTN-SR 500 mg (n=3) or ATX 80 mg and post-dose [123I]INER SPECT imaging. For SERT and DAT target occupancy evaluation, HVs received CTN-SR and post–dose [123I]β-CIT SPECT imaging at 200 (n=3), 500 (n=6) and 800 mg (n=6). Additional HVs (n=3) received MPH-LA 40 mg and post-dose [123I]β-CIT SPECT.

NET occupancy of CTN-SR and ATX was calculated as percent reduction in BPND between baseline and post-dose SPECT imaging for applicable ROI (brainstem). SERT and DAT occupancy of CTN-SR and MPH was calculated as percent reduction in binding potential (BPND) between baseline and post-dose SPECT imaging for applicable regions of interest (ROI for SERT: thalamus, midbrain and brainstem; ROI for DAT: putamen and caudate). Correlation analyses were completed to evaluate the relationship between target occupancies and plasma concentrations.

Results: Oral CTN-SR (200-800 mg) was safe and well tolerated. CTN-SR penetrated the brain demonstrating dose-related occupancy on NET, SERT and DAT. NET occupancy was 14.6% for CTN-SR 500 mg and 16.0% for ATX 80 mg. SERT occupancy for CTN-SR was 1.8%, 12.8% and 30.0% for 200, 500 and 800 mg respectively; SERT occupancy for MPH-LA, as expected, was 4.3%. DAT occupancy for CTN-SR was 8.0%, 12.8% and 25.0% for 200, 500 and 800 mg respectively. DAT occupancy for MPH-LA 40 mg was 20.7%. SERT and DAT occupancy increased with dose and significantly correlated with plasma concentrations ($r2 = 0.70$, $p = 0.0001$; $r2 = 0.53$, $p = 0.003$, respectively for SERT and DAT).

Conclusions: These results provide evidence for dose-related brain occupancy for CTN-SR on NET, SERT and DAT suggesting a central mechanism of action via norepinephrine, serotonergic, and dopaminergic pathways for CTN-SR in HV subjects. In addition, NET occupancy at an equivalent level to that of a typical dose ATX and CTN-SR demonstrates similar DAT occupancy to that of a typical dose of MPH-LA. This data provides valuable information comparing CTN-SR to currently available therapeutics and to aid dose selection for future clinical trials.

DASOTRALINE: A NOVEL DRUG CANDIDATE BEING EVALUATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND BINGE EATING DISORDER

Robert Goldman[*1], Nga Tong[2], Tracy Wetter[2], Kenneth S. Koblan[1], Seth C. Hopkins[1], Antony Loebel[1]*

[1]Sunovion Pharmaceuticals, Inc., Marlborough, MA and Fort Lee, NJ, [2]Sunovion Pharmaceuticals, Inc.

of special interest to clinicians

Abstract: Dasotraline is being evaluated by Sunovion Pharmaceuticals as a novel drug candidate for treating symptoms of Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents, and adults, and Binge Eating Disorder (BED) in adults.
Numerous stimulant and non-stimulant medications are available to treat ADHD, but their limited duration of effect may lead to inadequate symptom control before morning dosing and after the drug effect wears off later in the day. PK spikes that occur with each dosing interval can result in symptom rebound, while rapid surges in catecholamines induce effects that may be associated with drug abuse liabilities. Dasotraline may be a potential new therapeutic option for ADHD. It is a potent inhibitor of human dopamine (DA) and norepinephrine (NE) transporters. The PK profile in adults demonstrates slow absorption (tmax, 10-12 h) and elimination (t½, 47-77 h), with continuous, 24-hour steady-state plasma concentrations achievable within 2 weeks. A phase 2, double-blind, fixed-dose study of 331 adults with ADHD receiving once-daily dasotraline (4 mg/d [n=114] or 8 mg/d [n=107]) or placebo (n=110) demonstrated significant LS-mean improvement in the primary endpoint (ADHD Rating Scale, Version IV total score) at Week 4 with 8-mg/d dasotraline vs placebo (-13.9 vs -9.7; P=0.019) and trend-level significance with 4 mg/d (-12.4; P=0.076). The most frequently reported adverse events (AE) were insomnia, decreased appetite, nausea, and dry mouth. Consistent with the its PK profile, a single-dose human abuse liability study in healthy adult recreational stimulant users showed no significant difference between 3 dasotraline doses (8, 16, and 36 mg) vs placebo for the primary endpoint (Drug Liking Visual Analog Score at time of peak effect [DL-VAS Emax]), and for most secondary endpoints. All dasotraline doses were associated with significantly lower DL-VAS Emax compared with methylphenidate (40 and 80 mg). Both 8- and 16-mg dasotraline doses demonstrated an incidence of AEs similar to placebo, with the exception of insomnia (higher with 8- and 16-mg dasotraline doses) and headache (higher with 16-mg dose). AE incidence was higher with the 36-mg dose, though this is higher than the anticipated maximum therapeutic dose. For pediatric patients with ADHD, a single-dose study of 105 patients (6-17 y) showed a PK profile similar to adults, with slow absorption (median tmax 9.6-12 h) and elimination (t½ 56-84 h). Further, 2-4 mg/d doses in pediatric patients would yield exposures equivalent to 4-8 mg/d doses in adults. Studies assessing dasotraline at an additional dose in adults and dasotraline efficacy/safety in pediatric patients are underway.

Dasotraline may also be a potential new therapeutic option for BED. Non-clinical and clinical studies implicate dysregulated DA and NE circuitry as contributing to the BED etiology. Given the overlap between dasotraline DNRI pharmacology and BED neurobiology, studies are underway to evaluate once-daily dasotraline (4-8 mg/d) as a potential treatment option for moderate-to-severe BED in adults.

In summary, dasotraline provides continuous inhibition of DA and NE reuptake and has a low potential for abuse based on the human abuse liability study. Available clinical data add to the growing evidence of dasotraline as a potential new therapeutic option for the treatment of ADHD in children, adolescents, and adults, and moderate-to-severe BED in adults.

A PHASE 1 SINGLE- AND MULTIPLE-RISING DOSE STUDY OF THE SAFETY & PK OF EMB-001, A POTENTIAL TREATMENT FOR SUBSTANCE USE DISORDERS, WITH EXPLORATORY EFFICACY MEASURES IN TOBACCO USE DISORDER

of special interest to clinicians

Michael Detke[1], Carol Gloff[2], Gary Connor[2], Sherry McKee[3], Frank Greenway[4], Mark Leibowitz[5], Julie Straub[2], Ann Robbins[2], Doug Feltner[2], Nicholas Goeders[6]*

[1]Indiana University School of Medicine, [2]Embera NeuroTherapeutics, [3]Yale University, [4]Pennington Research Center & LSU, [5]CNS Network, [6]LSU Health Sciences Center

Abstract: Introduction: EMB-001 is a combination of two FDA-approved drugs: metyrapone (MET), a cortisol synthesis inhibitor, and oxazepam (OX), a benzodiazepine. MET is approved for only one day of use as a test of pituitary function; OX is approved for acute and chronic treatment of various anxiety disorders. EMB-001 reduced cocaine and nicotine self-administration and attenuated cocaine and methamphetamine cue reactivity in rats. In a human study in cocaine-dependent subjects, EMB-001 significantly reduced cocaine use.

Methods: This was a single- and multiple-rising dose study. Healthy volunteers who were daily cigarette smokers aged 18-65 were recruited; this population is relevant for studying both tobacco use disorder and cocaine use disorder, as 75-80% of the latter also smoke cigarettes. They received a single am dose on Day 1, BID dosing on Days 3-9 and a single am dose on Day 10. Three sequential dose cohorts of 8 subjects (6 drug, 2 placebo) received the following doses of MET and OX, respectively: 270 and 12 mg; 540 and 24 mg; and 720 and 24 mg. Total daily doses were double these amounts on BID dosing days, which were still low relative to FDA-approved maximum daily doses of both drugs. Primary outcomes were safety and the pharmacokinetics of MET, its active metabolite metyrapol, and OX. Safety measures included vital signs, ECGs and standard safety labs. Cortisol and other HPA axis parameters were monitored closely throughout the study. In addition, exploratory measures of efficacy in smoking cessation were assessed. Cigarettes smoked, breath CO and urine cotinine were assessed. The Smoking Urges Questionnaire and the Minnesota Nicotine Withdrawal Symptoms scales were administered prior to the start of BID dosing on day 3, and on the last day of BID dosing after a 12-hr enforced abstinence from smoking. The study was not powered for these efficacy assessments.

Results: The most frequent adverse event was somnolence. Most AEs were mild; all were mild or moderate. There were no SAEs and no discontinuations due to AEs. Serum cortisol was reduced 2-4 hours after the first dose, consistent with the known pharmacology of MET, but had returned to baseline on subsequent mornings and at follow-up; there were minimal to no symptoms suggesting adrenal insufficiency and ACTH stimulation tests were normal. There were no clinically significant changes in vital signs, ECGs or other safety labs. The half-lives of MET, OX and metyrapol were approximately and respectively 2, 7.5 and 8 hr. Exposure increased with increasing dose and there was modest accumulation with repeated dosing. There were reductions in cigarettes smoked, smoking urges and withdrawal symptoms, and although there was large variability, few systematic dose-related effects and most findings did not reach statistical significance in this small study, the Cohen's d effect sizes were moderate, ranging from .31 - .47.

Conclusions: EMB-001 was well-tolerated in this study and no new safety signals were identified. These findings are generally consistent with MET and OX approved labeling and with safety data in 6 published studies in which MET doses of 500-4000 mg/day were given for 2-8 weeks. PK results suggest that twice-daily dosing may provide appropriate duration of exposure for efficacy. Effects on smoking were encouraging for a small study that was not

powered for efficacy. Future plans include Phase 1b and 2 studies in cocaine use disorder and/or tobacco use disorder.

A RANDOMIZED PLACEBO-CONTROLLED MULTICENTER TRIAL OF A LOW-DOSE BEDTIME SUBLINGUAL FORMULATION OF CYCLOBENZAPRINE (TNX-102 SL*) FOR THE TREATMENT OF MILITARY-RELATED PTSD

Gregory Sullivan[1], Judith Gendreau[1], R. Michael Gendreau[2], Amy Schaberg[3], Bruce Daugherty[1], Heather Jividen[1], Ashild Peters[1], Perry Peters[1], Seth Lederman[1]*

[1]Tonix Pharmaceuticals, Inc., [2]Gendreau Consulting, [3]Schaberg Consulting

Abstract: Background: With only two agents, both selective serotonin reuptake inhibitors (SSRIs), FDA-approved for the treatment of posttraumatic stress disorder (PTSD), and no clear evidence of efficacy of any SSRI in clinical studies of US military personnel or veterans, there is a need for improved pharmacotherapy interventions for the disorder. TNX-102 SL is a low dose formulation of the tricyclic molecule cyclobenzaprine that has been designed for bedtime administration and sublingual absorption, with bypass of first-pass hepatic metabolism. Based on the multifunctional activity of cyclobenzaprine, which has with 5-HT2A serotoninergic, alpha1-adrenergic, and H1-histaminergic receptor blocking properties, TNX-102 SL is hypothesized to improve global symptoms of PTSD through therapeutic effects on sleep disturbance and hyperarousal. Study TNX-CY-P201 (the 'AtEase Study') is being conducted in order to assess for the efficacy, safety, and tolerability of TNX-102 SL in the treatment of PTSD in a population with primarily military-related traumas. Methods: In this multicenter, 12-week, double-blind study, adults meeting a DSM-5 diagnosis of PTSD as assessed by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) were recruited by advertisement and randomized to TNX-102 SL 2.8 mg, 5.6 mg, or Placebo in a 2:1:2 ratio. Patients were enrolled at 24 sites in the US. Eligible participants (males and females) were 18-65 years of age, had experienced DSM-5 PTSD Criterion A-qualifying trauma(s) during military service since 2001, had at least a moderate level of PTSD severity as indicated by a CAPS-5 score > 28, and were free of antidepressants for at least 2 months and free of or washed off other psychotropic medications. Exclusion criteria included serious suicide risk, unstable medical illness, substance use disorders within the prior 6 months, and lifetime history of bipolar 1 or 2, psychotic disorders, obsessive compulsive disorder, or antisocial personality disorder. The primary efficacy endpoint is the mean change from baseline in the CAPS-5 severity score between the TNX-102 SL 2.8 mg and placebo groups. Secondary endpoints include the PTSD Checklist for DSM-5 (PCL-5), Montgomery-Asberg Depression Rating Scale, Clinical and Patient Global Impression scales (CGI-I, PGIC), PROMIS Sleep Disturbance, CAPS-5 symptom cluster scores, and the Sheehan Disability Scale (SDS). A dynamic randomization procedure was employed to minimize trial-wide imbalances between the three treatment arms by site, sex, and presence (yes/no) of current comorbid major depressive disorder. CAPS-5 raters were MA-level or above in mental health fields who underwent a rigorous training and certification process. Sample size was powered to detect a 10-point difference between the Placebo and the TNX-102 SL 2.8 mg groups on the CAPS-5, considered a clinically relevant difference.

Results: A total of 245 participants were enrolled between January 2015 and December 2015. The results of primary topline analyses, including safety and tolerability information, will be presented.

of special interest to clinicians

Discussion: It is hypothesized that TNX-102 SL is a potentially effective, well-tolerated pharmacological intervention for the treatment of PTSD that works via effects on sleep disturbance and hyperarousal. The implications of the study results on further drug development and clinical practice in PTSD will be discussed.

Trial Registration: NCT02277704 Safety and Efficacy Study of TNX-102 SL in Subjects with Military-Related PTSD and Related Conditions

*TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

PERSEVERE: A STUDY OF ESKETAMINE FOR THE RAPID REDUCTION OF THE SYMPTOMS OF MAJOR DEPRESSIVE DISORDER, INCLUDING SUICIDAL IDEATION, IN SUBJECTS ASSESSED TO BE AT IMMINENT RISK FOR SUICIDE

Carla Canuso[1], Jaskaran Singh[2], Maggie Fedgchin[1], Larry Alphs[3], Rosanne Lane[1], Christine Pinter[1], Husseini Manji[1], Wayne C. Drevets[2]*

[1]Janssen Research & Development, [2]Neuroscience TA, Janssen R & D, LLC, Janssen Pharmaceutical Companies of JNJ, [3]Janssen

Abstract: Background: Major depressive disorder (MDD) is associated with an elevated rate of mortality, primarily due to suicide. The risk of suicide in those with MDD is about 20 times that of the general population, with over half of all suicides occurring in depressed individuals. While conventional antidepressants are often effective in treating depressive symptoms including suicidal ideation (SI), their delayed onset of action significantly limits their utility in the treatment of patients with MDD who are at imminent risk of for suicide. Recently, several studies of ketamine and esketamine have demonstrated that these agents can improve symptoms of depression in individuals with MDD within hours of administration. Additionally, preliminary studies of ketamine suggest it may have a similarly rapid effect in significantly reducing SI in subjects with MDD. As such, Janssen R&D is developing intranasal esketamine for the rapid reduction of the symptoms of MDD, including SI, in patients who are assessed to be at imminent risk for suicide.
Methods: PeRSEVERe is a recently completed 12-week, randomized, double-blind, placebo-controlled, multicenter Phase 2 study of intranasal esketamine in 68 adult subjects with MDD who are assessed to be at imminent risk for suicide. Included subjects had active SI and intent, and were in need of inpatient psychiatric hospitalization. The primary objective is to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in reducing the symptoms of MDD, including SI, as measured by the change from baseline on the MADRS total score at 4 hours post-dose on Day 1. Secondary efficacy objectives include the assessment of single and repeated doses of intranasal esketamine compared with intranasal placebo on the clinician's assessment of suicide risk as measured by the Suicide Ideation and Behavior Assessment Tool, and the subject's report of the severity in SI as measured by the Beck Scale for Suicide Ideation, through the end of the double-blind (DB) treatment and follow-up phases. Safety objectives include the assessment of transient perceptual changes, sedation, nasal tolerability, vital signs and suicidal thinking and behavior.

The study consists of a 24-48 hour screening evaluation performed prior to the Day 1 intranasal dose, immediately followed by a 25-day DB treatment phase, and a 56-day follow up phase. Given the vulnerability of the patient population, the study was conducted in the context of standard clinical care, with all subjects receiving standard antidepressant medication and initial in-patient hospitalization.

of special interest to clinicians

Results: PeRSEVERe is the first multi-center, prospective, placebo-controlled trial of a rapidly acting antidepressant in subjects with MDD who are assessed to be at imminent risk for suicide. The study, which was conducted at 11 centers in the United States, recently completed enrollment. Preliminary efficacy and safety results from the DB treatment phase will be available for presentation.

Conclusion: PeRSERVERe is the first multi-center placebo-controlled study of a potential rapidly acting antidepressant in patients with MDD who are assessed to be at imminent risk for suicide. Should study results be positive, esketamine may offer hope and a new paradigm of treatment for depressed patients at risk for suicide.

SRX246: A FIRST-IN-CLASS VASOPRESSIN 1A RECEPTOR ANTAGONIST IN PHASE II TRIALS FOR MOOD AND BEHAVIORAL DISORDERS

Neal Simon[1], Shi-fang Lu[1], Debra Itzkowitz[1], Eve Damiano[1], Christophe Guillon[2], Ned Heinde[3], Michael Brownstein[1]*

[1]Azevan Pharmaceuticals, Inc., [2]Azevan Pharmaceuticals, Inc. & Lehigh University, [3]Lehigh University

Abstract: SRX246 is a first-in-class, high affinity, high selectivity V1a receptor antagonist that is orally bioavailable. The compound represents a novel mechanism of action for treating disorders of stress, mood, and behavior. Currently, it is in clinical development for Intermittent Explosive Disorder, irritability/aggression in Huntington's Disease, and PTSD. In preclinical studies that included neuroimaging investigations, SRX246 was efficacious in models of fear, aggression, depression, stress, and anxiety. Safety, tolerability, and pharmacokinetic results in Phase I strongly supported continued development. A translational human Experimental Medicine fMRI study confirmed robust CNS effects and demonstrated proof-of-mechanism after oral dosing in circuits that are dysregulated in stress-related disorders. Analyses of post-mortem human brains showed that the target V1a receptor is present in limbic system and cortex and also is expressed at normal levels in post-mortem Huntington's Disease brains.

Three well-powered Phase II trials are in progress. The first is a Phase II trial with SRX246 for the treatment of Intermittent Explosive Disorder; enrollment has been completed and results are expected late in Q2 2016. The two additional Phase II trials will begin enrollment during the first half of 2016: one in irritable Huntington's Disease patients that will explore tolerability, safety, and activity with support from NINDS through the NeuroNext network, and another for the treatment of PTSD supported by the DoD. There are currently no approved treatments for Intermittent Explosive Disorder or irritability in Huntington's Disease. Two repurposed antidepressants are approved for PTSD, but these drugs are minimally effective. Vasopressin 1a receptor antagonism potentially represents a new approach that can address the unmet need in these indications as well as for other psychiatric disorders (e.g., treatment resistant depression). The development of SX246 at Azevan Pharmaceuticals has been supported by the National Institutes of Health through multiple SBIR grants, the National Toxicology Evaluation Program, the RAID Program, the NINDS NeuroNext program; through a grant from the Dept. of Defense; and private venture capital.

DRUG DEVELOPMENT STRATEGIES FOR SCHIZOPHRENIA USING A NOVEL PDE10A INHIBITOR: TAK-063

Tom Macek[1], Paul Goldsmith[2], Max Tsai[1], Maggie McCue[1], John Affinito[1], Kazunori Suzuki[3], Haruhide Kimura[3]*

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Abstract: Background: Translational Phase I studies are important to establish key information about a compound such as demonstration of adequate exposure at the target site of action, binding to the pharmacological target, and demonstration of pharmacological activity to prevent costly Phase II/III failures.
In preclinical studies, TAK-063 doses that achieved ~ 30% occupancy of phosphodiesterase 10A (PDE10A) in striatum produced antipsychotic-like effects, enhanced cognitive function, normalized pre-pulse inhibition, and reversed ketamine-induced increases in gamma power.

To date, no PDE10A inhibitor has shown clinical efficacy in the treatment of schizophrenia; therefore, relationships between preclinical and clinical effects have not been established. The TAK-063 phase I program aimed to obtain this information to be used for phase 2 dose selection.

Methods: Four Phase 1 clinical trials were conducted, covering a range of doses from 3 to 1000 mg. Two were placebo-controlled, double blind, dose-escalation studies (single and multiple dose). The single dose study included Japanese and non-Japanese healthy subjects. The multiple dose study included schizophrenia subjects and Japanese healthy subjects. A single-dose PET study to evaluate target occupancy of TAK-063 was conducted. A randomized, placebo-controlled, 3-period, incomplete crossover study evaluated the effects of single doses of TAK-063 on ketamine-induced changes in fMRI. In all studies, appropriate safety and PK were assessed. Most studies also included exploratory measures of cognition, EEG, and other biomarkers from preclinical studies.

Results: TAK-063 was safe and generally well tolerated in all studies. There were no serious adverse events (AEs). Single doses of TAK-063 were well tolerated up to 1000 mg in healthy subjects. Somnolence was the most common AE. Exposure was dose-proportional up to 30 mg, with a half-life suitable for once-daily dosing. Food increased absorption. In the MRD study, TAK-063 (given with food for 7 days) was tolerated at all doses. At 30 mg and above, more moderate to severe AEs were observed in schizophrenia subjects. Though a maximum tolerated dose was not defined, somnolence was potentially dose-limiting. Modeling explored relationships between plasma concentrations and AEs. Restoration of gamma synchrony with increases in alpha and decreases in slow waves were seen in electroencephalographic recordings most consistently at 20 mg.

Single doses of TAK-063 reversed the ketamine-induced increases in BOLD signal in brain regions in which risperidone has previously shown to have similar effects. The largest and most consistent effects on BOLD were observed in the 30 mg group, which approximates steady-state exposures of 20 mg.

A relationship between plasma concentrations and target occupancy in putamen was observed in the PET study. Using the occupancy data, a dose of 20 mg is predicted to achieve an average target occupancy greater than 30% at steady-state.

of special interest to clinicians

Based on these results, 20 mg was considered to be the highest, best tolerated dose that achieved relevant target occupancy, exposures, and produced consistent effects on exploratory biomarkers.

Discussion: These data provide an understanding of the safety, pharmacology, and PK of TAK-063. Based on these data, a proof of concept study has been initiated to determine the efficacy of 20 mg of TAK-063 administered nightly with food in the treatment of schizophrenia.

PHASE 2 STUDY OF BREMELANOTIDE IN PREMENOPAUSAL WOMEN WITH FEMALE SEXUAL DYSFUNCTIONS: RESPONDER ANALYSES BASED ON MINIMUM CLINICALLY IMPORTANT DIFFERENCES DERIVED FROM RECEIVER OPERATING CHARACTERISTIC CURVES

*Stanley Althof**[1], Johna Lucas[2], Raymond Rosen[3], Robert Jordan[2], Sally Greenberg[4], Leonard R. DeRogatis[5]*

[1]Case Western Reserve University School of Medicine, [2]Palatin Technologies, Inc.,[3]New England Research Institutes, Inc.,[4]S. Greenberg Statistical Consulting Inc., [5]Maryland Center for Sexual Health

Abstract: Background: Bremelanotide (BMT) is a novel cyclic heptapeptide known to act as a melanocortin-receptor-4 agonist and is in development to treat women with female sexual dysfunctions (FSDs).

Objectives: Post hoc responder analyses using receiver operating characteristic (ROC) curves were conducted to evaluate key efficacy outcomes in a large phase 2 study of BMT in premenopausal women with FSDs. The 5 key efficacy endpoints included the 4-week number of satisfying sexual events (SSEs), the total score and desire subscore on the Female Sexual Function Index (FSFI), and the total score and desire subscore on the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO).

Material and Methods: All patients were premenopausal, nonpregnant women ≥21 years old with hypoactive sexual desire disorder, female sexual arousal disorder, or both. Patients completing a 4-week baseline period of single-blinded subcutaneous (SC) placebo self-administration were then randomized to a 12-week treatment period of double-blind SC placebo or BMT 0.75-, 1.25-, or 1.75-mg dose for at-home, as-needed self-administration. The change from baseline to the end of the study of the key efficacy endpoints were calculated from patient responses to a questionnaire, which included an item asking: "To what degree do you think you benefited from taking the study drug?" The questionnaire used a 7-point Likert scale with choices ranging from 1 ("very much worse") to 4 ("no change") to 7 ("very much better"). A rating of 5 to 7 indicated a responder (i.e., patient-reported global benefit).

The minimum clinically important difference (MCID) was computed as the value simultaneously maximizing the endpoint's sensitivity and specificity for predicting a rating of 5 to 7 using an ROC curve for each of the 5 efficacy endpoints. The MCIDs were the anchors for the responder analyses.

Results: Responses from 327 patients provided data (for SSEs, n=324). The computed MCIDs were +1.0 for number of SSEs, +2.1 for FSFI total score, +0.6 for FSFI desire subscore, –7.0 for FSDS-DAO total score, and –1.0 for FSDS-DAO desire subscore. Using

these cut-offs, the SSE responder rate was 37% for placebo versus 38%, 48%, and 55% for BMT 0.75, 1.25, and 1.75 mg, respectively. The FSFI responder rate was 46% versus 45%, 61%, and 69%, respectively, for total score and 53% versus 46%, 60%, and 77%, respectively, for the FSFI desire subscore. The FSDS-DAO responder rate was 45% versus 49%, 60%, and 69%, respectively, for total score and 45% versus 48%, 57%, and 72%, respectively, for FSDS-DAO distress subscore. For all 5 endpoints, the difference from placebo was statistically significant for the BMT 1.75-mg dose ($P < 0.05$, Cochran-Mantel-Haenszel test).

Conclusions: There was a dose-dependent increase in responder rates of patients who self-administered SC BMT. The MCIDs for multiple FSD measures, which are widely used and clinically relevant, attained statistical significance in patients who self-administered the BMT 1.75-mg dose compared with placebo. Phase 3 studies to further evaluate SC BMT for the treatment of premenopausal women with FSD are in progress (ClinicalTrials.gov identifiers NCT02338960 and NCT02333071).

Study supported by: Palatin Technologies, Inc.

4:15 p.m. - 5:30 p.m.

Individual Research Reports

Substance Use Disorders, Treatments for Alzheimer's Disease, and Speeding Drug Discovery

PHARMACOGENETICS OF DOPAMINE BETA HYDROXYLASE IN COCAINE DEPENDENCE THERAPY WITH DOXAZOSIN

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Dave Nielsen, Daryl Shorter, Coreen Domingo, Thomas Kosten

Abstract: Background: Norepinephrine (NE) has two important reasons for being a treatment focus in cocaine use disorder (CUD): (a) NE appears to be functionally coupled to the dopamine (DA) system, making it a necessary component of the rewarding and reinforcing effects of cocaine, and (b) NE activity is linked with stress-induced reinstatement of drug-seeking behavior and is a likely component of the craving process. We examined doxazosin, an alpha 1 NE receptor antagonist for CUD treatment efficacy and for pharmacogenetic modulation of this efficacy by the gene coding for dopamine beta hydroxylase (DBH). The enzyme DBH is critical metabolic link that converts DA to NE. This gene for DBH has a promoter polymorphism that substantially reduces DBH enzyme levels and the conversion of DA to NE by about 10-100 fold. We hypothesized that doxazosin's effects on CUD treatment outcome would only be significant in those CUD patients with the normal rather than very low levels of DBH related to this polymorphism, because of the low levels of NE produced by DBH in those with this variant.
Methods: This 15-week, double-blind, placebo-controlled trial randomized 76 CUD patients to receive either doxazosin (8mg/day) (n=47) or placebo (n=29) and assessed urines for cocaine 3 times weekly. Patients were also genotyped for a functional promoter variant of the DBH gene with 49 patients in the dominant and 27 in the recessive group. This DBH polymorphism substantially reduces DBH enzyme levels and the conversion of DA to NE by about 10-100 fold.

Results: We found that cocaine-positive urines were significantly reduced with doxazosin compared to placebo with doxazosin dropping 25% and placebo increasing from baseline (medication effect, F=9.40, df=1, 2392; p=0.002) (time by medication, F=8.96, df=1, 2392; p=0.003). For the DBH alleles, the dominant group showed a significantly greater decrease in cocaine use (F=5.3; p<0.02), while the recessive group showed no difference.

Conclusions: Doxazosin response for CUD appeared to be pharmacogenetically mediated by this DBH polymorphism with the responder patients having the normal rather than substantially reduced DBH enzyme levels.

Learning Objectives:

- Doxazosin, an alpha-1 adrenergic receptor antagonist, significant reduced cocaine use in patients with cocaine use disorder.
- Efficacy of doxazosin was pharmacogenetically mediated by the polymorphism of dopamine beta hydroxylase.

Literature References:

- Kosten TR, Wu G, Huang W, Harding MJ, Hamon SC, Lappalainen J, Nielsen DA: Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β-hydroxylase. Biol Psychiatry. 2013;73:219-224
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GHRELIN AS A NOVEL POSSIBLE TARGET TO TREAT ALCOHOL CRAVING AND ROLE OF ENDOGENOUS HORMONES SERUM LEVELS AS A BIOMARKER

Carolina Haass-Koffler, Brown University

Danielle Giovenco, Mary Lee, Suzanne de la Monte, William Zywiak, George Kenna, Robert Swift, Lorenzo Leggio

Abstract: Increasing evidence supports the role of appetite-regulating pathways in alcoholism. In this set of studies, we tested the hypothesis that intravenous (IV) exogenous ghrelin administration acutely decreases endogenous serum leptin and insulin levels. Additionally, we explored possible correlations between changes in endogenous hormone serum levels and alcohol craving.

This was a double-blind, placebo-controlled human laboratory study. Non-treatment-seeking, alcohol-dependent, heavy-drinkers (n = 45) were randomized to receive IV ghrelin or placebo, followed by a cue-reactivity procedure, during which participants were exposed to neutral (juice) and alcohol trial cues. To determine the change in hormone levels, blood samples were collected at baseline and during the entire cue-reactivity experiment.

There was a main effect for IV ghrelin administration, compared to placebo, in reducing serum leptin levels [*P <.05]. Post hoc analysis showed significant differences in serum leptin levels at the alcohol trial [*P <.05] that persisted at the end of the experiment [*P <.05]. By contrast, there were no significant differences in serum leptin levels at the juice trial [P > .05]. This effect was specific for leptin, since there were no significant effects for IV ghrelin on other serum adipocytes levels analyzed, i.e.: resistin or visfatin [P > .05]. We found also a main effect for IV ghrelin, compared to placebo, in reducing serum insulin levels [*P <.05] and a time effect [**P < .001], but not ghrelin x time interaction [P > .05]. The

change of serum insulin levels parallel a similar trend in reducing connective-peptide (C-peptide) levels in the ghrelin group compared to placebo [P = .076]. No similar effects were found for other incretins here analyzed, i.e.: glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) [P > .05]. The reduction of serum leptin level at the alcohol trial negatively correlated with the increase in alcohol urge [p <.05], while urge to drink juice was not correlated with the leptin change at the juice trial [P > .05]. We did not find a correlation between the reduction of serum insulin and alcohol craving during the cue-reactivity experiment [P > .05].

Our findings represent the first human evidence that exogenous IV ghrelin administration results in reduction of endogenous serum leptin levels. Although ghrelin was found to reduce insulin level in alcohol-dependent individuals, the reduction of insulin did not correlate with changes in alcohol craving during the cue-reactivity procedure. We provided unique, yet preliminary evidence of ghrelin – leptin cross-talk in alcoholic individuals. We suggest that their relationship may play a role in alcohol craving and specifically changes in serum leptin levels can be used as possible biomarker to assess alcohol craving.

Learning Objectives:

- Evaluate serum leptin levels as a possible biomarker to assess alcohol craving and medication response. These results hold important clinical value because craving may be associated with relapse and has been proposed as a clinically relevant endophenotype able to predict alcohol-related outcomes. The topic of this study is also consistent with the theme of this year's ASCP meeting on new targets and integrative biomarkers.
- Objective 1, Alcohol craving specific: the correlation between ghrelin-induced changes in leptin and craving was specific for the urge to drink alcohol, as similar results were not found for the urge to drink juice.
- Objective 2, Peptide specific: the correlation was specific for leptin, as no similar results were found for insulin, other adipocytes or other incretins.
- Additional Note, Population specific: although this study did find an effect of intravenous ghrelin on leptin levels in a population of AD patients, it is important to note that in a previous small study with healthy controls, intravenous ghrelin did not change leptin levels.

Literature References:

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IMPACT OF CONCOMITANT ANTIDEPRESSANT USE ON DRINKING AND MOOD OUTCOMES IN BIPOLAR ALCOHOLICS: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL OF LAMOTRIGINE

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Abstract: Background: Alcohol use disorders are extremely common in people with bipolar disorder and are associated with a more severe illness course, poor treatment adherence, increased utilization of treatment resources, and roughly double the risk of attempted and completed suicides. Despite the prevalence and impact of alcohol use disorders in patients with bipolar disorder, few treatment trials have been conducted in this clinical population. The use of antidepressants in bipolar disorder remains controversial but is not uncommon in clinical practice. Given the complex relationship between drinking and mood stability in co-occurring alcohol dependence and bipolar disorder, the impact of antidepressant treatment on drinking and/or mood outcomes in those with both disorders is unclear and has received minimal study.

Aims: Data from a 12 week double-blind, randomized, placebo-controlled clinical trial of the anticonvulsant lamotrigine in alcohol-dependent adults with bipolar disorder were analyzed to compare the course of weekly drinking and mood symptoms in subjects who were treated with (+AD) vs. without (-AD) concomitant antidepressants at the time of enrollment.

Methods: Adults aged 18-65 who met DSM-IV criteria for bipolar I or II disorder and current alcohol dependence were eligible if stably maintained on an approved mood stabilizing agent (lithium or second-generation antipsychotic(s)). Mood symptoms were assessed with the Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI-II), and Young Mania Rating Scale (YMRS). Quality of life measures included the LIFE-RIFT and SF-12. Quantity and frequency of drinking (Timeline Follow-Back) and craving (Obsessive-Compulsive Drinking Scale (OCDS)) were recorded weekly over 12 weeks. Changes in mood and drinking outcomes (drinks/week, drinks/drinking day, heavy drinking days, percent days abstinent, craving scores) were analyzed by general linear models using treatment assignment (lamotrigine vs placebo) and baseline severity of drinking and mood symptoms as co-variates.

Results: Of 43 subjects enrolled, n=36 returned for at least one visit after randomization and n=25 completed all weekly assessments. At enrollment, 41% of the subjects reported taking prescribed antidepressants (+AD; 92% SSRIs). Whereas no significant differences were evident between groups in number of hospitalizations, previous suicide attempts, or baseline depression symptoms, age of onset of bipolar disorder was significantly earlier, and baseline YMRS scores were significantly higher, in -AD subjects compared with +AD subjects. No significant differences in baseline drinking, craving, alcoholism severity, age of onset of alcoholism, duration of longest abstinence, or days since last drink were detected between +AD vs. -AD groups. Similarly, the two groups did not differ significantly in the course of drinking outcomes over the 12 weeks of the study, though a trend toward heavier drinking at Week 4 and Week 5 in +AD subjects was appreciated.

Conclusions: In actively-drinking alcohol-dependent adults with bipolar disorder enrolled in a 12 week randomized controlled trial of lamotrigine, subjects currently taking concomitant antidepressants had later onset of bipolar disorder and lower baseline levels of (hypo)manic symptoms relative to their counterparts not treated with antidepressants. No clear effects of concomitant antidepressants were evident in the course of drinking outcomes over 12 weeks in this sample, though small sample size as well as the self-report nature of drinking and concomitant medication adherence are among the limitations of the study.

Learning Objectives:

- Recognize clinical characteristics associated with adjunctive antidepressant use in bipolar patients with co-morbid alcoholism.

of special interest to clinicians

- Explore the impact of concomitant antidepressant treatment on course of mood and drinking outcomes in a sample of alcohol-dependent bipolar patients assessed weekly over a 12-week clinical trial.

Literature References:

- Frye MA, Salloum IM (2006) Bipolar disorder and comorbid alcoholism: prevalence rate and treatment considerations. Bipolar Disord 8: 677-85.
- Pettinati HM, O'Brien CP, Dundon WD (2013) Current status of co-occurring mood and substance use disorders: a new therapeutic target. Am J Psychiatry 170: 23-30.

THE CODING AND NONCODING TRANSCRIPTIONAL LANDSCAPE OF NEURONS AND GLIA IN VIVO

Adarsh Reddy, Trinitas Regional Medical Center

David O'Brien, Nilambari Pisat, Claire Weichselbaum, Kristina Sakers, Miriam Lisci, Jasbir Dalal, Joseph Dougherty

Abstract: Background: Studies in psychiatric genetics have identified over 100 loci associated with disease risk, yet many of these loci are distant from protein coding genes. Recent characterization of the transcriptional landscape of cell lines and whole tissues has suggested widespread transcription in both coding and non-coding regions of the genome, including differential expression from loci that produce regulatory non-coding RNAs which function within the nucleus.

Methods: Here we have defined the nuclear transcriptional landscape of the three major cellular divisions of the nervous system using flow sorting of genetically labeled nuclei from bacTRAP mouse lines. This was followed by characterization of the unique expression of coding, non-coding and intergenic RNAs in the mature mouse brain with RNAseq and validation with independent methods.

Results: Our findings reveal diverse expression across the cell-types of all classes of RNAs, including long non-coding RNAs – several of which were confirmed as highly enriched in the nuclei of specific cell-types using anatomical methods. Finally, we also discovered several examples of cell-type specific expression of tandem gene fusions, and report the first cell-type specific expression of circular RNAs, notably a neuron specific and nuclear enriched RNA arising from the gene Hnrnpu.

Conclusion: The methods described in the study can be utilized to identify novel targets of psychotropic agents in a celltype-specific manner.

Learning Objectives:

- To educate the audience about how genomic approaches could be potentially utilized to identify novel mechanisms of action of psychotropic agents.
- To familiarize audience to the concept of non-coding RNAs.

Literature References:

- Adarsh Reddy, David O'Brien, Nilambari Pisat, Claire T. Weichselbaum, Kristina Sakers, Miriam Lisci, Jasbir Dalal, Joseph D. Dougherty: The coding and noncoding transcriptional landscape of neurons and glia in vivo. Biological Psychiatry (Accepted for publication pending minor revisions in written manuscript)
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translational profiling approach for the comparative analysis of CNS cell types. Cell 2008; 135:749–762

EFFECT OF RENAL AND HEPATIC IMPAIRMENT ON THE PHARMACOKINETICS OF ENCENICLINE

Gordon Loewen, FORUM Pharmaceuticals

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Abstract: Introduction: Encenicline (ENC) is an orthosteric α7 nicotinic acetylcholine receptor agonist in development for the treatment of cognitive impairment in schizophrenia and Alzheimer's disease. Studies were conducted to evaluate the effect of renal (RI) and hepatic (HI) impairment on the pharmacokinetics (PK) of ENC and its metabolites (ENC N-oxide [ENO] and ENC acid metabolite [EAM]).

Methods: In separate studies, ENC (1.8 mg free base as an oral tablet) was administered to subjects with mild (n=12), moderate (n=9), or severe (n=8) RI (based on Cockcroft–Gault estimation and the FDA RI categories), subjects with mild (n=8), moderate (n=8), or severe (n=8) HI (based on Child–Pugh categorization) and age- and BMI-matched healthy control subjects. Plasma samples were collected up to 288 hours postdose and were assayed for ENC and metabolite concentrations using a validated HPLC-MS/MS method. Treatment-emergent adverse events (TEAEs) and vital signs were collected throughout the study. PK parameters were determined using standard non-compartmental methods. Ratios of least squares mean (LSM) PK parameters for the impairment groups relative to the control group and the associated 90% confidence intervals were determined.

Results: ENC area under the plasma concentration curve (AUC) and elimination half-life (t1/2) increased and renal clearance (CLr) and oral clearance (CL/F) decreased with increasing severity of RI. Based on geometric LSM ratios, ENC AUC was 37%, 63%, and 153% higher, CLr was 31%, 64%, and 73% lower, and CL/F was 27%, 39%, and 61% lower in subjects with mild, moderate, and severe RI, respectively, compared with the control group. ENC PK was only moderately affected by HI. Based on geometric LSM ratios, ENC AUC was within 8% of control in subjects with mild and moderate HI and was 24% higher than control in subjects with severe HI. ENO and EAM AUC and t1/2 increased with increasing severity of RI, with the magnitude of the effect of RI severity on metabolite exposure being greater (up to 883% increase) than that for ENC. ENO and EMA AUC were generally lower in subjects with HI. ENC free fraction in plasma was ~10-11% in control subjects and subjects with RI or HI. For ENC and its metabolites, significant negative correlations were observed between CLcr and AUC and positive correlations were observed between CLcr and CL/F or CLr. In the RI study, 13 TEAEs were reported by 7 subjects, with the majority (n=8) of TEAEs reported by subjects in the severe RI group. TEAEs occurring in more than 1 subject were nausea and vomiting (2 subjects; both severe RI), back pain (2 subjects; 1 each in control and severe RI), and headache (2 subjects; 1 each in moderate and severe RI). In the HI study, 3 TEAEs were reported (upper respiratory tract infection and anemia in severe HI, and back pain in controls); none was considered related to ENC. In both studies, most changes in laboratory endpoints and vital signs were considered not clinically significant, or were consistent with underlying disease. No clinically significant changes in ECGs were observed.

of special interest to clinicians

Conclusions: Encenicline exposure increases with increasing degree of RI but is minimally affected by HI. The clinical significance of these observations and the potential need for dose adjustments in patients with RI are currently being evaluated.

Learning Objectives:

- To understand the effect of mild, moderate, or severe renal or hepatic impairment on encenicline pharmacokinetics.
- To understand the effect of mild, moderate, or severe renal or hepatic impairment on the encenicline safety profile.

Literature References:

- Barbier AJ, et al: Pharmacodynamics, pharmacokinetics, safety, and tolerability of encenicline, a selective α7 nicotinic receptor partial agonist, in single ascending-dose and bioavailability studies. Clin Ther 2015; 37(2):311-324.
- Keefe RS, et al: Randomized, double-blind, placebo-controlled study of encenicline, an α7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. Neuropsychopharmacology 2015; 40(13):3053-3060.

Improving Assessment and Clinical Trial Methodology

HOW DO KEY CO-PRIMARY MEASURES OF FUNCTIONAL CAPACITY PREDICT REAL WORLD FUNCTION IN SCHIZOPHRENIA?

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Alexandra Atkins, Vicki G. Davis, Philip Harvey, Meera Narasimhan, Tom Patterson

Abstract: Introduction: Patients with schizophrenia have profound and disabling cognitive deficits that interfere with multiple aspects of daily functioning. Indeed, research suggests that cognitive impairment accounts for more disability in real world functioning than any other aspect of the illness, including psychosis (e.g. August, 2012). In order to assess the potential impact of cognitive enhancement therapy on functioning, the FDA has required that clinical trials for cognitive impairment in schizophrenia demonstrate improvement on a standard performance-based cognitive assessment, as well a co-primary measure of 'functional capacity' that can serve as an intermediary between cognitive and functional improvement, and may signal increased potential for improved outcomes. Although the relationship between cognitive performance and standard measures of functional capacity have been well-described, less attention has been devoted to the relationship between functional capacity and measures of real world function. In order explore this, we examined the relationship between real world function and performance on three measures of functional capacity, including the University of California San Diego Performance-Based Skills Assessment (UPSA-VIM), the Schizophrenia Cognition Rating Scale (SCoRS) and Virtual Reality Functional Capacity Assessment Tool (VRFCAT).

Methods: Participants included 158 patients who met DSM-IV TR criteria for schizophrenia. Participants were recruited as part of a non-treatment psychometric validation study conducted across three research sites, including the University of South Carolina, the University of Miami - Miller School of Medicine, and the University of California, San Diego.

All subjects completed the MATRICS Consensus Cognitive Battery (MCCB), UPSA-VIM, SCoRS and VRFCAT at the same study visit. Real world function was evaluated using the

Specific Levels of Functioning (SLOF; Schneider & Struening, 1983). The same informant was used for both the SCoRS and SLOF measures. The SLOF dependent variable for the statistical analyses was the total score across the all subscales. Correlations between the SLOF, MCCB composite score and each measure of functional capacity were assessed using Pearson correlation coefficients.

Results: All three measures of functional capacity demonstrated significant correlations with SLOF total score. Consistent with prior findings, the correlation between cognition (MCCB) and real world function as measured by the SLOF was modest but significant, r=.33, p<.001. Of the three functional capacity measures, the SCoRS demonstrated the strongest correlations with the SLOF, r=-.57 (p<.001), a finding likely influenced by informant input to both measures. The SCoRS correlation with the MCCB was r=-.42 (p<.001). UPSA-VIM correlations with the SLOF and MCCB were r=.27 (p=.002) and r=.70 (p<.001), respectively. The VRFCAT also demonstrated significant correlations with the SLOF, r=.23 (p=.007) for total time and r=.35 (p<.001) for total errors. Correlations between the VRFCAT and MCCB composite were r=.57 and r=.39 for total time and total errors, respectively (p<.001 for both).

Conclusions: Current measures of functional capacity in schizophrenia demonstrate modest-to-moderate correlations with assessment of real world function. Performance-based functional capacity measures have stronger correlations with performance based measures of cognition, while the interview-based measure of functional capacity had a stronger correlation with a real-world functional scale. Results are consistent with the conception of functional capacity as a potential mediator of the relationship between cognition and real world function.

Learning Objectives:

- Recognize the importance of functional capacity assessment in schizophrenia.
- Examine the relationship between measures of functional capacity and real world functioning.

Literature References:

- August SM, Kiwanuka, J. N., McMahon, R. P., Gold, J. M. The MATRICS Consensus Cognitive Battery (MCCB): clinical and cognitive correlates;. Schizophrenia Research. 2012;134:76-82.
- Green M, Schooler, N., Kern, R., Frese, F., Granberry, W., Harvey, P., Karson, C., Peters, N., Stewart, M., Seidman, L., Sonnenberg, J., Stone, W., Walling, D., Stover, E., Marder, S., Evaluation of Functionally Meaningful Measures for Clinical Trials of Cognition Enhancement in Schizophrenia. American Journal of Psychiatry. 2011;168:400-407.

DO SUICIDALITY PHENOMENA FOLLOW A LINEAR OR A NON-LINEAR PROGRESSION OVER TIME?

David Sheehan, University of South Florida College of Medicine

Jennifer M Giddens

Abstract: Background: It is assumed that suicidality progresses from suicidal ideations (passive suicidal ideation, then active suicidal ideation) to suicidal behaviors (suicidal preparatory behaviors, then suicide attempts). This model of progressive, linear suicidality has been the basis of much research into risk and protective factors for suicidality.

Understanding the true nature of suicidality over time will help researchers build better predictive models.
Methods: Methods developed by Robert Stetson Shaw, a physicist at UCSC to analyze data from an oscillator in 2- and 3-dimensional space (2D and 3D, respectively) were used. These methods are used in non-linear dynamics theory / non-linear systems theory / turbulence theory / deterministic chaos. We adapted his methodology to an analysis conducted on 3 databases collected from the same subject over time. One is a database of over 43,000 events of suicidality captured using T-CASA. The other two databases were collected over 145 weeks, using S-STS and SPTS.

Results: The method used permitted the mathematical graphic modeling of suicidality phenomena over 3 years in the form of 2D- and 3D-attractors. The results found a non-linear dynamic relationship of suicidality phenomena over time. There was no progressive, linear relationship of suicidality phenomena over time.

Conclusions: The relationship of suicidality phenomena over time is non-linear and dynamic. To improve predictive models of suicidality, the progressive, linear models need to be abandoned in favor of non-linear, dynamic systems mathematical modeling that more accurately reflect the turbulence, the apparent unpredictability, and the dynamic nature of the complex system of suicidality.

Learning Objectives:
Following this presentation, participants will be better able to:

- Understand that suicidality may not follow a linear progression, but follows a model of chaos dynamics.
- Appreciate the need to consider non-linear dynamic systems mathematical modeling when building predictive models of suicidality.
- Understand that most (if not all) research on risk and protective factors for suicidality are based on linear models and may not accurately model the true non-linear dynamic nature of suicidality.

Literature References:

- Sheehan, DV and Giddens, JM. 2015. Suicidality: A Roadmap for Assessment and Treatment. Available from: http://www.HarmResearch.org
- Shaw R. The dripping faucet as a model chaotic system. Ariel Press. 1984.

IS IT POSSIBLE TO REDUCE BIASES AND INACCURACIES IN LARGE SCALE CLINICAL TRIALS?

Mark Opler, ProPhase LLC

Jonathan Rabinowitz

Abstract: To achieve regulatory approval and marketing permission novel drugs often undergo world-wide trials frequently at tens and hundreds of individual sites. Not surprisingly the quality of data varies radically from site to site. Occasionally, investigators have biased study data and results due to carelessness, wishful thinking, currying favor or even malicious intent. Patients may try to please investigators, exaggerate or under report benefits and adverse effects or even participate in the same trial at more than one site. CNS trials are particularly vulnerable due to lack of biological markers and reliance on subjective rating scales and self-reported data. Because Effect Size(s) of psychiatric treatments is relatively small, even few errors/biases can lead to incorrect results and/or failed studies. In

the current economic climate study failures can lead to the permanent abandonment of potentially beneficial treatments.
The presentation will present examples of pre-planned consistency checks that can be conducted "on line" during the trial and can reduce such biases and inaccuracies. The idea is to build logical algorithms of rating data and provide researchers at sites with "on line" feedback regarding potential illogical rating. Examples of inconsistencies for the PANSS, MADRS and other scales from very large data bases of the NEWMEDS project will be presented. Presentation will include a set of consistency checks to be used within and across measures.

Learning Objectives:

- Participant will learn how to check for consistency and accuracy in reporting using consistency flags.
- Participant will learn how to use consistency checking in real time to reduce errors.

Literature References:

- Gwet, K. L. 2014. Intrarater Reliability. Wiley StatsRef: Statistics Reference Online.
- Kemp AS, Schooler NR, Kalali AH, Alphs L, Anand R, Awad G, Davidson M, Dube S, Ereshefsky L, Gharabawi G, Leon AC, Lepine JP, Potkin SG, Vermeulen A. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophr Bull. 2010;36:504-509.

NINE PROBLEMS IN THE DESCRIPTIONS OF THE PSYCHIATRIC INCLUSION AND EXCLUSION CRITERIA IN PUBLICATIONS OF ANTIDEPRESSANT EFFICACY TRIALS

Mark Zimmerman, Brown University

Matthew Multach, Emily Walsh, Lia Rosenstein, Douglas Gazarian, Heather Clark

Abstract: Objective: The inclusion and exclusion criteria used to select patients into antidepressant efficacy trials (AETs) has received relatively little scrutiny and discussion. More than a decade ago we found that most patients in an outpatient practice presenting for the treatment of major depressive disorder (MDD) would not have qualified for an AET, a result that was replicated by other investigators. We had recently wondered whether the concerns about the generalizability of AETs that were expressed more than 10 years ago had an impact on the psychiatric inclusion/exclusion criteria used in more recent studies. In conducting our literature review there were a number of instances in which the descriptions of the inclusion/exclusion criteria were imprecise or vague and therefore difficult to interpret. Methods: We conducted a literature review that included a search of the Medline (via PubMed), Embase (via ovid), and Psychinfo (via Ebsco host) databases and identified 170 placebo-controlled AETs that were published between 1995 and 2014.

Results: In conducting our literature review we identified 9 areas where inclusion/exclusion criteria are poorly described: exclusion of bipolar disorder, exclusion of psychotic symptoms, exclusion of substance use disorders, exclusion of personality disorders, exclusion of any comorbid disorder, exclusion of patients with a primary nondepressive disorder, exclusion due to suicide risk, time frame of exclusions, and HAMD cutoff. Specific examples of each type of problem will be described.

Conclusion: Because of the heterogeneity and vagueness in describing the inclusion/exclusion criteria AETs we recommend the adoption of a standardized method of presenting a study's inclusion and exclusion criteria.

Learning Objectives:

At the conclusion of the session, the participant should be able to:

- Describe specific problems with the descriptions of the inclusion and exclusion criteria of antidepressant efficacy trials.
- Recognize ways of improving the description of the inclusion and exclusion criteria of antidepressant efficacy trials.

Literature References:

- Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice. Am J Psychiatry. 2002;159:469-473
- Zimmerman M, et al. Have treatment studies of depression become even less generalizable?: A review of the inclusion and exclusion criteria in placebo controlled antidepressant efficacy trials published during the past 20 years. Mayo Clin Proc. 2015;90:1180-1186.

VALIDATION OF THE TABLET-BASED BRIEF ASSESSMENT OF COGNITION (BAC APP) FOR SCHIZOPHRENIA

Brian Saxby, NeuroCog Trials

Alexandra Atkins, Vicki G. Davis, Tina Tseng, Adam Vaughan, Philip Harvey, Meera Narasimhan, Tom Patterson, Richard S.E. Keefe

Abstract: Introduction: Computerized tests benefit from automated scoring procedures and standardized administrator instructions. These methods can reduce the potential for rater error. However, especially in patients with severe mental illnesses and neurologic disorders, the equivalency of traditional and tablet-based tests cannot be assumed. The Brief Assessment of Cognition in Schizophrenia (BACS) is a pen-and-paper cognitive assessment tool that has been used in hundreds of research studies and clinical trials, and has normative data available for generating age- and gender-corrected standardized scores. A tablet-based version of the BACS called the BAC App has been developed. This study compared performance on the BACS and the BAC App in patients with schizophrenia and healthy controls. Test equivalency was assessed, and the applicability of paper-based normative data was evaluated.

Methods: Participants included 48 patients (23 female) with schizophrenia and 50 healthy controls (25 female) recruited from three academic sites including the University of California-San Diego, the University of Miami - Miller School of Medicine, and the University of South Carolina. All participants were assessed with the standard pen-and-paper BACS and the BAC App.

Results: In both groups, the distributions of standardized composite scores for the tablet-based BAC App and the pen-and-paper BACS were indistinguishable, and the between-methods mean differences were not statistically significant. The discrimination between patients and controls was similarly robust with the BAC App (d=1.34) and the BACS (d=1.24). The between-methods correlations for individual measures in patients were r>0.70 except Token Motor (r=0.43) and Tower of London (r=0.61). In patients, performance

between the test methods was not significantly different on any test except the Token Motor Test. When data from the Token Motor Test were removed, the between-methods correlation of composite scores improved to r=.88 (df=48; P<.001) in healthy controls and r=.89 (df=46; P<.001) in patients, consistent with the test-retest reliability of each measure.

Conclusions: The tablet-based BAC App generates results consistent with the traditional pen-and-paper BACS. These data support the notion that the BAC App can now be used in clinical trials and clinical practice.

Learning Objectives:

- Examine methods for determining task equivalence between pen-and-paper and computerized cognitive assessments.
- Describe the validity and usability of a tablet-based cognitive test battery for use in schizophrenia.

Literature References:

- Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 2004;68:283-297.
- Keefe RS, Harvey PD, Goldberg TE, Gold JM, Walker TM, Kennel C, Hawkins K. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr Res. 2008;102:108-115.

Mood Disorders: Targets, Approaches, and Outcomes

MOODNETWORK: AN INNOVATIVE APPROACH TO PATIENT-CENTERED CARE

Andrew Nierenberg, Massachusetts General Hospital

Louisa G. Sylvia, Thilo Deckersbach, Casey M. Hearing, Alexandra K. Gold, Roberta Tovey, Anthony Debenedictis, Allen Doederlein, Susan Edgman-Levitan, Muffy Walker, Donna Holland Barnes, Jonathan Alpert, Jordan Smoller, Marlene Freeman, David Rubin

Abstract: MoodNetwork, a part of the Patient Centered Outcomes Research Network (PCORnet), aims to gather 50,000 individuals with mood disorders to provide longitudinal data through patient reported outcomes to improve mood disorder treatment. MoodNetwork provides opportunities for patients to participate in comparative effectiveness research and engage in all stages of research – from setting priority questions, determining the main outcomes, governance and oversight of studies, to dissemination of results with the goal of enhancing participants' sense of empowerment and agency through unprecedented collaboration with the research community. MoodNetwork team is a collaboration of clinicians, researchers, patients, caregivers, members, and advocacy group partners (Depression and Bipolar Support Alliance, International Bipolar Foundation, Anxiety and Depression Association of America, National Organization for People of Color Against Suicide, and National Alliance on Mental Illness).

Participants sign on-line informed consent to join research studies and offer feedback on future research study ideas and outcomes. Participants can ask questions of expert clinicians and engage in blogs and forums on topics related to mood disorders. Participants are offered the Quick Inventory of Depressive Symptomatology (16-Item), Depression and Bipolar Support Alliance Wellness Tracker, WHO-5 Well-Being Index, Experience of Care and

Health Outcomes Survey, Altman Self Rated Mania Scale, Mini International Neuropsychiatric Interview Depression, and the Composite International Diagnostic Interview Mania. All participants provide demographic information such as gender, race, and presence of mood symptoms.

MoodNetwork has enrolled over 2000 participants between June and November 2015. Of the participants, 96.0% report experiencing depression and 81.4% endorse having mania or hypomania. The mean age is 43.3 (SD=38.4). Of the sample, 77.2% of participants are female, 19.8% are male, and the remaining report ambiguous or other/unknown gender. 932 participants are employed, 475 are disabled, 413 are unemployed, 232 are students, 232 are homemakers, 213 are volunteers, and 173 are retired. Participants represent 50 states, 5 territories, and 43 countries. The racial and ethnic breakdown of the participants is as follows: 84.3% White, 5.4% Multiple race, 4.0% Asian, 3.2% unknown, 2.4% Black, African American, African, or Afro-Caribbean, and 0.7% Native American, American Indian, or Alaskan Native. Participants (N=1,003) identified reducing stigma (11.5%), alleviating symptoms (11.0%), and reducing barriers to care (9.6%) as the top three research priorities.

MoodNetwork's places participants at the center as equal partners in research.

Learning Objectives:

- To review the importance of establishing a patient-centered online infrastructure to conduct comparative effectiveness research and to discuss engagement strategies to include patients in the research process.
- To explore the utility of online tools for the treatment of mood disorders.

Literature References:

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A GENOME WIDE ASSOCIATION STUDY IMPLICATES GABAERGIC NEUROTRANSMISSION IN EARLY ONSET BIPOLAR DISORDER

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Abstract: Background: Although multiple genes have been implicated in bipolar disorder (BD), they explain only a small proportion of its heritability. Identifying additional risk variants may be hampered by BD heterogeneity, which is usually not taken into account in genome-wide association studies (GWAS). BD with early age at onset is a more homogeneous familial form of the disorder associated with greater symptom severity. Methods: We conducted a GWAS of early-onset BD (onset of mania/hypomania ≤19 years old) in a discovery sample of 419 cases and 1033 controls and a replication sample of 181 cases and 777 controls. These two samples were meta-analyzed, followed by replication of one signal in a third independent sample of 141 cases and 746 controls.

of special interest to clinicians

Results: No single nucleotide polymorphism (SNP) associations were genome-wide significant in the discovery sample. Of the top 15 SNPs in the discovery analysis, rs114034759 in the muskelin (MKLN1) gene was nominally significant in the replication analysis, and was among the top associations in the meta-analysis (p=2.63E-06, OR=1.9). In the third sample, this SNP was again associated with early-onset BD (P=0.036, OR=1.6). Gene expression analysis showed that the rs114034759 risk allele is associated with decreased hippocampal MKLN1 expression.

Conclusion: Our results suggest MKLN1 is associated with early-onset BD. MKLN1 regulates cellular trafficking of GABA-A receptor, which is involved in synaptic transmission and plasticity, and is implicated in the mechanism of action of a group of antiepileptic mood stabilizers. These results therefore indicate that GABAergic neurotransmission may be implicated in early-onset BD.

Learning Objectives:

- Identifying genetic risk variants for complex disorders (such as Bipolar disorder) may be hampered by their heterogeneity, which could be addressed in genome-wide association studies (GWAS) with a narrower phenotype (i.e., early onset bipolar disorder).
- The importance of testing the initial genetic associations in multiple independent cohorts to confirm the finding.

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EARLY AND SUSTAINED WORK PRODUCTIVITY IMPROVEMENT PREDICTS SUBSEQUENT CLINICAL COURSE IN MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Lost work productivity accounts for most of the economic burden related to major depression. Antidepressant treatments improve work productivity; however, the long term effect of this improvement continues to be unclear. There is a need to systematically evaluate change in work productivity with antidepressant medications and test the association of changes in work productivity with long-term clinical course.
Methods: Using data from multiple visits of both acute- and continuation-phases of the Combining Medications to Enhance Depression Outcomes (CO-MED) trial, we estimated changes in work productivity, before and after controlling for change in depression severity and selected baseline clinical and sociodemographic variables. We measured work productivity at each visit with Work Productivity and Activity Impairment (WPAI) self-report in 331 employed participants with MDD. We then used data-driven longitudinal grouping to identify trajectories of changes in work productivity during first 6 weeks of treatment. We then tested the association of these groups with clinical improvement in follow-up periods of up to 7 months.

Results: As compared to baseline, reductions with time were statistically significant for all measures of work productivity – absenteeism ($F = 6.34$, degrees of freedom (df) = 7, $p < 0.0001$), presenteeism ($F = 22.82$, $df = 7$, $p < 0.0001$) and work productivity loss ($F = 22.85$, $df = 7$, $p < 0.0001$) after 12 weeks of antidepressant medication treatment even after controlling for changes in depression symptom scores at each visit and selected baseline variables. Three distinct groups based on the trajectory of change in work productivity at 6 weeks were identified: 1) robust early improvement (24% of the sample), 2) minimal change (49%), and 3) high impairment slight reduction (27%). After controlling for select baseline variables and remission status at week 6, the early improvement group had 3-5 times higher remission rates at 12 weeks and 2-6 times higher remission rates at 28 weeks than other groups.

Conclusion: Antidepressant medication treatment improves work productivity in depressed patients; this improvement is not fully accounted for by depressive symptom reduction. Early improvement in work productivity is associated with higher chances of symptom remission after 12 and 28 weeks of treatment.

Learning Objectives:

- To identify work productivity impairment in MDD patients as distinct from changes in depression severity.
- Understand the long-term clinical consequences of work productivity impairment.

Literature References:

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ADHERENCE AND PERSISTENCE ACROSS ANTIDEPRESSANT THERAPEUTIC CLASSES: A RETROSPECTIVE CLAIMS ANALYSIS AMONG INSURED US PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Abstract: Background: Guidelines recommend treatment of a presenting episode of Major Depressive Disorder (MDD) with antidepressant (AD) therapy for at least 4-9 months after achieving response. (1) Although previous studies suggest low adherence and persistence to ADs in the MDD population (2), there is still a clear gap in the current literature assessing adherence and persistence at clinically relevant time points and at the therapeutic class level. Previous studies also exclude newer ADs and formulations that have received approval in the past 10 years. This study includes newer ADs and formulations and assesses adherence and persistence to the AD medication, to the therapeutic class, and overall to AD therapy at multiple, clinically relevant, time points.

Methods: Truven Marketscan® Commercial, Medicare, and Medicaid databases were queried for MDD patients between the years 2003-2014. To ensure patients were newly diagnosed with MDD, a period, consisting of 6 months of continuous eligibility with no MDD diagnoses nor AD prescriptions, was required. Patients who initiated with one AD

prescription were identified from the following therapeutic classes: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and ADs with other mechanisms of action. Continuous insurance coverage was required from at least 6 months before through 12 months after the index AD prescription date. Proportion of Days Covered (PDC) was used to calculate adherence, ranging from 0.0 to 1.0, and dichotomized as adherent (PDC ≥0.80) or not adherent (<0.80). Persistence was defined as days until a 30-day gap in therapy. Adherence and persistence were calculated to: initial AD medication, initial AD therapeutic class, and AD therapy overall, over the first 3, 6, 9, and 12 months from the index prescription date. Multivariable logistic regression estimated the adjusted odds ratios (OR) of adherence to each time frame with initial SSRI therapy as the referent group and adjusted for demographic and clinical characteristics, as well as comorbid anxiety or chronic non-cancer pain disorders.

Results: Of 527,907 included patients, the proportions considered adherent to the initial AD medication decreased over 3, 6, 9, and 12 months (0.41, 0.31, 0.24, and 0.21). Similar patterns were observed for the proportions adherent to the initial AD therapeutic class (0.43, 0.33, 0.26, and 0.23) and to AD therapy overall (0.44, 0.35, 0.29, and 0.26). Persistence was similar to adherence estimates across all time points. The multivariable logistic model estimated that compared to SSRIs, the odds of a patient adhering to initial AD medication when initiating with an SNRI were 20%-27% greater at 3 months (OR 1.20, 95% confidence interval [CI] 1.18, 1.22), 6 months (OR 1.23, 95% CI 1.21, 1.25), 9 months (OR 1.25, 95% CI 1.22, 1.27), and 12 months (OR 1.27, 95% CI 1.24, 1.30); (p-values all <0.0001). Patients who were prescribed an initial AD from other classes had either similar or significantly lower odds of adherence, when compared to SSRIs.

Conclusion: We found low adherence and persistence to ADs in the MDD population. Adherence differs by therapeutic class, with patients initiating SNRI therapy having a higher likelihood of adherence.

Learning Objectives:

- To describe adherence and persistence to AD therapy for MDD patients.
- To understand the likelihood of adherence to initial AD medication.

Literature References:

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VILAZODONE INHIBITING PRO-INFLAMMATORY GENE EXPRESSION AND IMMUNOLOGIC ACTIVATION COMPARED TO PAROXETINE IN GERIATRIC DEPRESSION

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Abstract: Objectives: We performed a pilot study of vilazodone, a novel antidepressant never tested in geriatric depression, compared to a gold-standard drug used in geriatric depression, paroxetine. This pilot study is designed to determine whether there are any difference in the effects sizes between vilazodone and paroxetine, and to assess comparative tolerability in older depressed adults. We also examined genomic markers of inflammation and telomerase activity in the two groups to explore potential biomarkers of response. Methods: Participants: Fifty-six non-demented older adults diagnosed with major depression were randomized to receive vilazodone [N=26] or paroxetine [N=30].

Interventions: A 12-week double-blind trial of vilazodone vs paroxetine. Paroxetine daily doses ranged between 10-30 mg (mean = 27.20, SD = 6.78, range = 10-30); Vilazodone effective daily dose was 40 mg per day 10-40 mg. Genomic markers of inflammation and group differences in tolerability and safety were explored.

Results: There were no baseline differences between the groups in demographic and clinical variables. Effect size estimates indicate that overall the Vilazodone group subjects show increased improvement in mood compared to Paroxetine (on HAMD -2.25 vs -1.31), accompanied by greater improvement in Health-related Quality of life (SF-36 scales).

However, Paroxetine group showed greater improvement in several cognitive measures compared to Vilazodone with significant differences in the measures of attention and executive function. Of the 17 completers in the paroxetine group reported mild side-effects (mean of 1.4 (SD=1.2)) and 16 reported some side-effects, with a mean of 1.4 (SD=1.2) side-effects without observed group differences. A markedly greater decrease over time in expression of pro-inflammatory indicator genes for Vilazodone-treated patients compared to Paroxetine-treated patients (p = .0294) was found.

The Vilazodone group had greater improvement in depression and quality-of life, the paroxetine group had greater improvement in the several cognitive measures of attention and executive function.

Conclusion: The Vilazodone group showed a significant effect in inhibiting pro-inflammatory gene expression and immunologic activation in relative to the paroxetine group, which may contribute to the pathophysiology of depression. This pilot trial should inform future larger trials of geriatric depression.

Learning Objectives:

- To learn about group difference in clinical response to Vilazodone vs Paroxetine in geriatric depression.
- To learn about the effect of Vialzodone vs Paroxetine on genomic markers of inflammation.

Literature References:

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of special interest to clinicians

Advances in Schizophrenia*

PREVALENCE, RISK FACTORS AND OUTCOME OF METABOLIC SYNDROME IN VETERANS WITH SERIOUS MENTAL ILLNESS

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Abstract: Objectives: To assess the prevalence of metabolic syndrome and compare patient characteristics and outcomes by metabolic syndrome status among Veterans with serious mental illness (SMI) in a retrospective cross-sectional study.
Methods: Veterans with schizophrenia/schizoaffective disorder or bipolar disorder receiving psychiatric and medical treatment in VISN 4 facilities during 10/1/2010─9/30/2012 were identified. Prevalence of metabolic syndrome using modified National Cholesterol Education Program criteria (≥3 of following conditions: diabetes/pre-diabetes, dyslipidemia, hypertension, overweight/obesity) was assessed. "Index" antipsychotic drugs were defined as an antipsychotic prescribed for at least 30 days and for the greatest number of days during the study period for a given patient. Differences in demographic and clinical characteristics, treatments, healthcare utilization, and mortality stratified by metabolic syndrome status were compared using Chi-square or Student's t tests; odds ratios (OR) with 95% confidence intervals (CI) for risk factors of metabolic syndrome were derived from a multivariate logistic regression analysis.

Results: Among 10,132 Veterans with SMI, 4,958 (48.9%) met criteria for metabolic syndrome. Veterans with metabolic syndrome were more likely to be male (OR=1.75, 95%CI=1.52-2.02), African-American (OR=1.26, 95%CI=1.12-1.41) and married (OR=1.16, 95%CI=1.05-1.28) compared to those without metabolic syndrome (all p<.005). In addition, they were more likely to receive a 50%-100% service-connected pension than be assigned to a low-income category (OR=1.16, 95%CI=1.04-1.28, p=.006) and showed a trend for not being homeless (OR=0.91, 95%CI=0.81-1.02, p=.09). Those with metabolic syndrome were more likely to be diagnosed with schizophrenia/schizoaffective disorder (OR=1.22, 95%CI=1.03-1.45), bipolar depression (OR=1.18, 95%CI=1.06-1.32), or post-traumatic stress disorder (OR=1.59, 95%CI=1.14-2.23) (all p<.05). Veterans with metabolic syndrome were more likely to receive at least a 30-day supply of antipsychotics (OR=1.23, 95%CI=1.12-1.36), antidepressants (OR=1.60, 95%CI=1.46-1.76), or mood stabilizers (OR=1.29, 95%CI=1.17-1.41) (all p<.0001), and had a higher rate of receiving 2 or more antipsychotics (23.3% vs. 19.7%, p<.0001). Among Veterans receiving index antipsychotics, 50.5% had metabolic syndrome while 44.6% had metabolic syndrome even among Veterans not receiving index antipsychotics (p<.0001). Veterans with metabolic syndrome had a higher mortality rate (7.1% vs. 5.7%) and triple the rate of coronary artery (19.0% vs. 5.9%) and cerebrovascular disease (9.1% vs, 2.8%) (all p<.01). They also had higher rates of emergency visits (11.3% vs. 9.8%) and psychiatric (16.7% vs. 13.8%) or medical hospitalizations (21.4% vs. 11.1%) compared to those without metabolic syndrome, but were less likely to be hospitalized for substance use disorders (6.9% vs. 8.6%) (all p<.05).

Conclusion: Nearly one in two Veterans with SMI had metabolic syndrome, which was strongly associated with adverse cardiovascular outcomes and high healthcare utilization.

of special interest to clinicians

Demographic, socioeconomic, and clinical characteristics were significant risk factors for metabolic syndrome, in addition to prescription of antipsychotics and other psychotropic drugs. More assertive, broad-based screening and monitoring of patients with SMI at high risk of developing metabolic syndrome is needed.

Learning Objectives:

- Participants will review data showing the importance of broad-based screening and monitoring of patient demographic, socioeconomic and clinical factors in addition to pharmacologic treatment factors in prediction of risk of metabolic syndrome.
- Participants will review data showing the strong association of metabolic syndrome with increased mortality, adverse cardiovascular outcomes and high healthcare resource utilization among Veterans with serious mental illness.

Literature References:

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- Olfson M, Gerhard T, Huang C, et al: Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry 2015; 72:1172-1181

RELATIVE EFFICACY AND SAFETY OF INDIVIDUAL SECOND-GENERATION ANTIPSYCHOTICS IN TREATING FIRST EPISODE PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Juan Gallego, Tianxu Xia, Delbert Robinson, Anil Malhotra, John Kane, Christoph Correll

Abstract: Background: Early treatment choice in first episode psychosis is important. Our previous meta-analysis compared the efficacy and tolerability of individual first-generation antipsychotics (FGAs) with second-generation antipsychotics (SGAs) (Zhang et al. 2013). SGAs are the predominant medications in treating psychosis in clinical practice. However, no systematic reviewed have examined the relative efficacy and safety of various SGA agents in treatment of first episode psychosis.

Methods: Meta-analysis was conducted on randomized, head-to-head trials comparing SGA medications in first episode psychosis, published by 10/31/2015. Random effects model was used to pool effect sizes, either Hedges' g for continues variables or risk ratio for dichotomous outcomes. Heterogeneity across studies and potential publication bias were examined. Primary outcomes were total psychopathology change, response rate and all-cause discontinuation. Secondary outcomes included specific-cause discontinuation, changes in positive and negative symptoms as well depression, and adverse effects.

Results: Literature search yielded 20 studies consisting of 2,995 patients comparing 7 SGAs (olanzapine, risperidone, Quetiapine, ziprasidone, aripiprazole, clozapine, and amisulpride). Pair-wise comparisons of individual SGAs were conducted. Clozapine and amisulpride were used in only one study each, therefore excluded from analysis. For total symptom reduction, olanzapine and risperidone were significantly better than quetiapine, Hedges'g = .20 (N=4) and .38 (N=5), respectively, p's<.05. No significant difference was found among other SGAs, although aripiprazole might have a small advantage over risperidone and ziprasidone, but these comparisons consisted of only two studies. No significant difference was found in response rate and all-cause discontinuation rates among included SGAs. Consistently, olanzapine and risperidone outperformed Quetiapine in reducing positive symptoms, but

there was no significant difference in reduction of negative symptom and depression among SGAs, except that aripiprazole was better than risperidone in treating negative symptoms in one study. For adverse effects, risperidone induced more extrapyramidal symptoms (EPS) than olanzapine while ziprasidone had worse EPS than quetiapine, Hedges' g = .23 (N=5) and .35 (N=2), respectively, p's<.05. Olanzapine was the worse in inducing weight gain than other SGAs, all p's<.05. Quetiapine was also worse in weight gain liability than ziprasidone, Hedges' g = .42 (N=3), p<.01.

Discussion: SGAs have variable efficacy and side effect profiles in treating first episode psychosis. While olanzapine, risperidone, and aripiprazole seemed to be more efficacious than quetiapine and ziprasidone, olanzapine and quetiapine induced more weight gain and risperidone was associated with higher EPS. Clinicians need to individualize treatment decisions, weighing different aspects of efficacy, tolerability, availability and cost.

Learning Objectives:

- Learn the current evidence on using second generation antipsychotics (SGAs) to treat first episode schizophrenia.
- Learn the relative efficacy and tolerability of various SGAs in treating first episode schizophrenia.

Literature References:

- Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2013;16:1205-1218.
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WORLDWIDE CLOZAPINE THERAPEUTIC DRUG MONITORING (TDM) FROM CAPILLARY BLOOD, USING THE DRIED BLOOD SPOT (DBS) TECHNIQUE: A MAJOR STEP FORWARD IN ADEQUATE DOSING AND TREATMENT OF THERAPY-RESISTANT SCHIZOPHRENIA.

Dan Cohen, Mental Health Organization North-Holland North

Lisanne Geers, Anton Loonen, Daan Touw

Abstract: Introduction: Clozapine is the drug of last resort in treatment-resistant schizophrenia. Clozapine-resistance should be avoided when possible. Therapeutic drug monitoring can assist in preventing clozapine-resistance. First by detecting clozapine non-compliance. Secondly, clozapine serum concentrations after equal dosages of clozapine were given to different patients have been shown to vary by a factor 6. This could easily result in pseudo-clozapine non-response in a subpopulation with too low (below threshold) clozapine plasma levels. This state of affairs will remain undetected as long as clozapine plasma levels are not measured. As many developed (Israel, Russia, Serbia) and underdeveloped (African) countries lack the facility of clozapine therapeutic drug monitoring (TDM), this is not a

theoretic possibility but a very common reality. The challenge was to develop a technique that enables clozapine TDM for clinical use in these countries.
Specific purpose: We decided to apply the technique of dried blood spots (DBS), that has been validated in TDM of tuberculostatics, for clozapine.

Methodology: Patients on stable clozapine treatment, in whom the clozapine dosage had remained unchanged for at least two weeks, were asked to participate.

Bloods sampling took place at baseline, 2, 4, 6 and 8 hours after clozapine intake.

At each of the 4 blood samplings, 3 samples were taken at the same time: regular venous samples, dried blood spot samples from regular venously sampled blood and dried blood spot samples form capillary sampled bloods.

Results: The participating 15 patients, mean age of 44 years, were predominantly male ((12/15) and smoking (10/14). DBS analysis showed good linearity over the concentration time curve measured. The accuracy and between- and within-day precision variation values, validated three times, were within accepted ranges. Different blood spot volumes and hematocrit values had no significant influence on the results. DBS samples were stable at room temperature (20º C) and 5 ºC for respectively two weeks and 3 days. The mean ratio of the clozapine concentration in DBS samples to that in plasma was 0.81 (95% CI 0.76 to 0.85).

Conclusion: The Dried Blood Spot (DBS) analysis is a reliable method for therapeutic drug monitoring (TDM) of clozapine in daily practice.

Importance: Clozapine DBS makes clozapine TDM worldwide available, which is especially important for countries that lack the facility for clozapine TDM.

Learning Objectives:

- Therapeutic drug monitoring (TDM) of clozapine from capillary using the dried blood spot (DBS) method is both feasible and reliable.
- DBS offers the opportunity of clozapine TDM facility for countries that lack the facility of clozapine TDM.

Literature References:

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SUCCESSFULLY OVERCOMING CLOZAPINE UNDERPRESCRIPTION: THE DUTCH APPROACH AS AN EVIDENCE-BASED MODEL FOR SCALING-UP INNOVATION AND GOOD PRACTICE ABROAD

Dan Cohen, Mental Health Organization North-Holland North

Jan Bogers, Daniel Van Dijk, Bert Bakker, Raphael Schulte

Abstract: For decades clozapine has been, and still remains, the only evidence-based treatment option for therapy-resistant schizophrenia, which is estimated to affect around 30% of the patient population with schizophrenia.
For decades, clozapine underuse has been documented, especially so in the USA which has exceptionally low prescription rates of 2%-4%. In the latest figures covering 45 states, in 2,5% of all the patients and 5,5 % of the treatment-resistant patients clozapine was initiated (Stroup 2014). A slightly larger study in 48 states looked into the prevalence of clozapine prescription: the prescription rates were 10%-16% in 6 states: South Dakota (15.6%), Connecticut (13.4%), Colorado (11.8%), Washington (11.4%), Vermont (10.7%) and Maine (10.2%), with a total population of 28 million inhabitants. The prescription rates in the other 42 states, with a total population of 290 million inhabitants, was below 10%. In the 4 most populated states, with a total population of 105 million inhabitants, prescription rates were 4% or below: Texas (3.8%), California (4%), Florida (3.2%) and New York (4%).

In the current situation, with a mean prescription rate of approximately 3%, one tenth of the patient population with therapy-resistant schizophrenia is being treated. Clozapine underprescription is therefore the rule, not the exception.

In the interest of the wellbeing of patients with therapy-resistant schizophrenia, who rank highly on the list of the most severely affected mentally ill patients, overcoming widely prevalent prescription impairments is of vital interest to all involved. In the first place the patients, their families and supportive system, their mental health care providers and last but not least the economic burden: greater severity of mental illness with more impairments, and therefore more needs, results in more intensive health care and simply costs more.

an effective strategy is required to combat this stubborn phenomenon. We present the Dutch approach.

In 2004, a Dutch group of 4 psychiatrists and 1 internist (affiliated with an inpatient psychiatric institution) have established the non-profit Dutch Clozapine Collaboration Group (DCCG) in order to increase the evidence-based and safe prescription of clozapine (www.clozapinepluswerkgroep.nl). This national clozapine expertise center has a fivefold task. It functions as oracle – free of charge - to mental health professionals on all questions that are somehow related to clozapine, such as treatment indications and initiation, prevention or treatment of side effects, the role of comedication etc.

Second, a clinical guideline for the use of clozapine has been developed, which covers divergent topics such as on- and off-label indications, clozapine titration schedules, criteria for an adequate clozapine trial, detection and treatment of both common and rare side effects, prevention of complications, and difficult clinical decisions, such as renewed prescription (rechallenge) after leukopenia, termination of mandatory white blood cell counts, and compulsory treatment. The guideline has since been incorporated into the national teaching program for residents in psychiatry, as advocated by Freudenreich. The Dutch and English guideline can be downloaded free of charge from the group's website.

Third, educating mental health professionals by lecturing to staff in mental health organizations, at congresses and other scientific meetings and by providing educational materials, such as patient information, algorithms for frequently encountered situations (sialorrhea, constipation, fever) or potentially dangerous situation (leucopenia, hyperglycemia). Fourth, the DCCG contributes to a modernization of the clozapine guideline to ensure it is in keeping with the latest findings and results. Fifth, the group initiates studies

that, due to technological innovations, can facilitate clozapine prescription and/or contribute to more evidence-based prescription. One such an example is leukocyte plus differentiation from capillary blood sampling on the spot by using a point of care device. Both patients and staff had a clear preference for this method of leukocyte monitoring (Bogers et al). A second study addressed the problem of therapeutic drug monitoring of clozapine plasma level. The new method of Dried blood Spots, which only requires a blood of capillary blood and a functioning postal system, has been validated for its application and implementation in clozapine therapy, thereby making clozapine TDM available worldwide.

That all being said, the key question is and remains whether all these efforts bore fruit, that is: did it result in increased prescription of clozapine? The answer is a definitive 'yes it did'. In its 10 years of existence, clozapine prescription in the Netherlands rose 56%, by far exceeding the 19% rise in prescription rate of the group of atypical antipsychotics (GIP databank). The answer is therefore that all these efforts did indeed bear fruit and did result in substantially increased use of clozapine, which was the main aim of all these combined efforts for all those years.

After 10 years, we can safely conclude that the strategy that was chosen by the DCCG has shown its positive effects in daily practice and that its approach is an effective and evidence-based method to combat clozapine underuse.

It is up to other countries, both policymakers and professionals, to benefit from this pioneering work by implementing this approach in a form such as that is fits the national and local situation.

Learning Objectives:

- Clozapine underprescription, the results of prescribers' fear, is the main obstacle in clozapine prescription and adequate treatment in therapy-resistant schizophrenia.
- The model of the Dutch Clozapine Collaboration Group offers an evidence-based model to successfully overcome clozapine underprescription.

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THRESHOLD OF DOPAMINE D2/3 RECEPTOR OCCUPANCY FOR HYPERPROLACTINEMIA IN OLDER PATIENTS WITH SCHIZOPHRENIA

Yusuke Iwata, CAMH Toronto

Shinichiro Nakajima, Fernando Caravaggio, Takefumi Suzuki, Hiroyuki Uchida, Eric Plitman, Jun Ku Chung, Wanna Mar, Philip Gerretsen, Bruce Pollock, Benoit H. Mulsant, David Mamo, Ariel Graff-Guerrero

Abstract: Objective: Although hyperprolactinemia carries a long-term risk of morbidity, the threshold of dopamine D2/3 receptor (D2/3R) occupancy for hyperprolactinemia has not been investigated in older patients with schizophrenia. This study included 42 clinically stable outpatients with schizophrenia (DSM-IV) (mean±SD age: 60.2±6.7 years) taking olanzapine or risperidone. Subjects underwent [11C]-raclopride positron emission tomography (PET)

scans to measure D2/3R occupancy before and after reducing their dose of antipsychotic by up to 40%. Blood samples were collected before each PET scan to measure prolactin (PRL) levels.
Method: The relationship between PRL and D2/3R occupancy was examined using stepwise linear regression analyses. The D2/3R occupancy thresholds for hyperprolactinemia were explored using Fisher's exact tests.

Results: PRL decreased following dose reduction (mean±SD, 24.1±30.2 to 17.2±15.1, $p<0.001$). 16 subjects showed hyperprolactinemia at baseline and 11 subjects still had hyperprolactinemia after dose reduction. PRL levels were associated with female gender ($\beta=0.32$, $p=0.006$, vs. male), antipsychotics ($\beta=0.23$, $P=0.02$, risperidone vs. olanzapine), and D2/3R occupancy ($\beta=0.23$, $p=0.04$). Those with D2/3R occupancy higher than 66% were more likely to have hyperprolactinemia than those with D2/3R occupancy lower than 66% ($p=0.03$). Sensitivity, specificity, positive predictive value, and negative predictive value of this threshold were 0.44, 0.81, 0.78, and 0.48, respectively. We identified a D2/3R occupancy threshold for hyperprolactinemia of 66% in older patients with schizophrenia that is lower than that in younger patients (~73%).

Conclusion: This is the first PET study to examine the relationship between the striatal D2/3R occupancy and PRL levels in older patients with schizophrenia, extending the age range of previous studies of younger patients reporting on the relationship between striatal D2/3R occupancy and PRL levels. Our results suggest a higher sensitivity to antipsychotics in older patients. Clinicians are advised to regularly monitor PRL levels and try to minimize exposure to antipsychotics while maintaining their clinical effectiveness in stable older patients with schizophrenia.

Learning Objectives:

- This is the first PET study to examine the relationship between the striatal D2/3R occupancy and PRL levels in older patients with schizophrenia, extending the age range of previous studies of younger patients.
- The D2/3R occupancy threshold for hyperprolactinemia in older patients with schizophrenia was 66%, which is lower than that reported for younger patients (~73%). Our results suggest a higher sensitivity to antipsychotics in older patients.

Literature References:

- Tsuboi T, Bies RR, Suzuki T, Mamo DC, Pollock BG, Graff-Guerrero A, Mimura M, Uchida H. Hyperprolactinemia and estimated dopamine D2 receptor occupancy in patients with schizophrenia: analysis of the CATIE data. Progress in neuro-psychopharmacology & biological psychiatry. 2013;45:178-182.
- Graff-Guerrero A, Rajji TK, Mulsant BH, Nakajima S, Caravaggio F, Suzuki T, Uchida H, Gerretsen P, Mar W, Pollock BG, Mamo DC. Evaluation of Antipsychotic Dose Reduction in Late-Life Schizophrenia: A Prospective Dopamine D2/3 Receptor Occupancy Study. JAMA psychiatry. 2015;72:927-934.

Wednesday, June 1, 2016

8:30 a.m. - 10:00 a.m.

Regulatory Plenary with FDA: Evolving Views on Pseudospecificity and Comparing Drug and Device Regulatory Pathways

of special interest to clinicians

Mark Rapaport, Emory University School of Medicine
Tiffany Farchione, FDA
William Heetderks, CDRH, FDA

Abstract: This year's plenary session will focus on two topics:

- The Division of Psychiatry Products' evolving stance on pseudospecificity.

  Historically, the Division has viewed a number of potential labeling claims (e.g., cognitive dysfunction associated with major depressive disorder) to be artificially narrow and, thus, pseudospecific. DPP is now more willing to consider indications that were previously deemed pseudospecific. Dr. Farchione will discuss the Division's current views, as well as trial design considerations for any development programs designed to evaluate an indication that was once considered pseudospecific.

- A comparison of the regulatory review process for drugs and devices.

  Representatives from both the Division of Psychiatry Products in the Center for Drug Evaluation and Research (Dr. Farchione) and the Division of Neurological and Physical Medicine Devices in the Center for Devices and Radiological Health (Dr. Heetderks) will compare and contrast the regulatory requirements and review processes in the two Centers as they related to the treatment of psychiatric illnesses.

10:15 a.m. - 11:15 a.m.

ASCP Lifetime Awardee Talk - Evidence in Clinical Psychiatry: 60 Years in Psychiatric Practice and Research

EVIDENCE IN CLINICAL PSYCHIATRY: 60 YEARS IN PSYCHIATRIC PRACTICE AND RESEARCH

John Davis, UIC Psychiatric Institute, Dept. of psychiatry, University of Il at Chicago, Chicago, IL

Abstract: When I wrote my first scientific papers 60 years ago, academic psychiatry was entirely psychoanalytic. Don Klein and I participated in the development of modern psychopharmacology, writing Diagnosis and the Drug treatment of Mental Disorders, which was both research and clinically based. Over the last 40 years, the clinical side has atrophied, and research is less clinically relevant. I will place modern research in historical prospective, with a focus interpretation of research to make it more clinically relevant. I will start with the application of pharmacology to understand mechanisms of how drugs produce improvement, the biologically-based theories of mental illness, and the clinical pharmacology of psychotropic drugs (such as drug metabolism or drug-drug interactions), updating this with current work in molecular biology. I performed, in 1975 the first meta-analysis in psychiatry; the second in general medicine, showing maintenance treatment prevents relapse, update this with recants network meta-analyses. I will summarize clinical evidence, provide prospective, but the focus is on how to apply clinical studies to individual patients, to tell sense from nonsense, and to the balance of benefit to risk. I will present the efficacy of psychotropic drugs in the perspective of drug used in internal medicine.

1:00 p.m. - 2:30 p.m.

Wednesday Afternoon Panel Sessions

DRINKING CHANGE, CONSEQUENCES, AND BIOMARKERS IN ALCOHOL CLINICAL TRIALS: RESULTS FROM THE ALCOHOL CLINICAL TRIALS INITIATIVE (ACTIVE)

Raymond Anton, Medical University of South Carolina

Overall Abstract: While a number of pharmacotherapy trials of alcohol use disorder have been completed and published, only 3 medications (disulfiram, naltrexone, and acamprosate) have been approved by the FDA for use in the US. One reason that pharmaceutical companies have been reluctant to development medications in this area is the lack of clarity on clinical trial methods, including appropriate "drinking endpoints". While change in alcohol consumption, however defined, clearly has to be considered as the primary endpoint in clinical trials, the relationship of this change in consumption to alteration in alcohol related consequences is paramount in understanding the clinical meaning of that change. Recently the European Medications Agency has accepted a change in drinking as a valid endpoint (based on WHO drinking risk criteria), even if some heavy drinking days occurred during treatment, while the FDA in the US has recently suggested that a "no heavy drinking day" endpoint would be acceptable. However, there is considerable uncertainty how drinking levels relate to consequences, particularly over the longer term. In addition, there is great interest in the use of biological markers to provide "objective" measurement of outcome in clinical trials. There are now three biomarkers of chronic (Serum Carbohydrate Deficient Transferrin - %CDT), sub-acute (Blood Phosphotidyl Ethanol – PEth) and acute (Urinary Ethylglucuronide – EtG) alcohol use that can be applied to clinical investigation and clinical trials.

The Alcohol Clinical Trials Initiative (ACTIVE) was formed as a public-private partnership including members of Academia, Industry, and Government (NIAAA, NIDA, and FDA) to better understand and define best methods/practices in alcohol clinical trials. While a number of issues are being addressed by ACTIVE, one of the most salient is the most appropriate "drinking endpoint" in alcohol clinical trials. For the FDA, EMA, and the clinical community to be comfortable with a choice of drinking endpoint, one important question needing to be addressed is how that level/change in drinking relates to drinking-related consequences (e.g. health, social, and employment). Also, a better understanding is needed of how biomarkers can assist in establishing the veracity of self-reported drinking and how they might relate to alcohol consequences.

The ACTIVE group, in conjunction with others outside of the workgroup, has attempted to gather relevant information from a number of sources on the relationship between various levels, or change in levels, of drinking and clinical consequences. Since there are a limited number of large clinical-trial data sets, this work has been expanded to include data available in epidemiological studies as well. The effort is focused on the use of data that has already been collected to evaluate how it might inform decisions regarding drinking endpoints in clinical trials.

This symposium will have 4 presenters and a discussant that will focus on data from alcohol clinical trials and epidemiological studies. Dr. Anton (MUSC) will introduce the symposium

and mention the structure of ACTIVE and its mission. Dr. Skeete (FDA) will provide the FDA view of drinking outcome endpoints and the reason to believe that drinking measures are only "surrogate markers" for the larger problem of alcohol use disorder and its consequences. Her presentation will also include the recent FDA draft guidance on endpoints for AUD clinical trials. Dr. Witkiewitz (Univ. of New Mexico) will present data from the re-examination selected large alcohol clinical trials (e.g. the COMBINE study (n=1383)) where the relationship between defined WHO drinking risk categories and drinking-related consequences (Drinker Inventory of Consequences (DrInC)) during treatment were evaluated. She will also contrast these findings with similar assessments done in a large epidemiological study (NESARC). Dr. Dan Falk (NIAAA) will evaluate how the WHO drinking risk categories can be applied to clinical trials. He will present data from an NIAAA conducted phase 2 study on Varenicline in Alcohol Use Disorder to show how change in the WHO category from "the beginning to the end of the trial" might be used to assess outcome. Dr. Ray Anton (MUSC) will overview the available drinking biomarkers and will provide examples from his work, and that of others, on how they might be used in clinical trials. Dr. Raye Litten (NIAAA) will summarize the data presented, as well as discuss future directions and goals of NIAAA and ACTIVE in pursuing data that will inform investigators, as well as the regulatory process, on the most appropriate drinking outcome measures for clinical trials.

Learning Objectives:

- Be able to recognize the current drinking endpoints in clinical trials of alcohol use disorder, especially the potential use of the change in WHO drinking risk criteria as it relates to alcohol drinking consequences.
- Increase knowledge of clinically available alcohol biomarkers (blood and urine lab tests) as they relate to various levels of drinking and how they can be used to supplement self-reported drinking in alcohol clinical research and trials.

FDA GUIDANCE ON DEVELOPING DRUGS FOR THE TREATMENT OF ALCOHOLISM

Rachel Skeete, Division of Anesthesia, Analgesia, and Addiction Products, Center for Drug Evaluation and Research, US Food and Drug Administration

Individual Abstract: Identification of appropriate outcome measures has proved a regulatory challenge in designing clinical trials for the treatment of alcoholism. Although considerable attention is given in clinical trials to various ways to collect and characterize alcohol consumption, drinking behavior itself, particularly observed during the brief window of a clinical trial, is a surrogate endpoint because measures of alcohol consumption are not direct measures of how the patient feels, functions, or survives. On the other hand, clinical trials demonstrating direct clinical benefit of drugs to treat alcoholism might need to be very long and very large, and consequently may be impractical. Therefore, FDA does not require that direct effects on the physical and psychosocial consequences of alcoholism be demonstrated during the brief window of a clinical trial; however, modifications in drinking behavior that are likely to translate to improvement in how the patient feels, functions, or survives should be shown.

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. Analyses of data from clinical trial populations and longitudinal observational studies commissioned

by NIAAA have resulted in support for defining patients who reduce their drinking to non-problematic levels and sustain that pattern for a meaningful period of time as treatment responders. As a result, the current recommendation for clinical trials of products to treat alcoholism 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:

- Discern/recognize the use of drinking behavior in alcoholism clinical trials as a surrogate endpoint, and understand the bases for identifying valid surrogates for clinical benefit and the challenges in defining reduction endpoints.
- Describe the FDA's current recommendations for clinical trials to support marketing of drugs to treat alcohol dependence.

Literature References:

- Alcoholism: Developing Drugs for Treatment. Guidance for Industry. Draft Guidance. February 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm433618.pdf

THE RELATIONSHIP OF WHO DRINKING RISK CATEGORIES TO ALCOHOL CONSEQUENCES: CONSISTENCY IN POPULATION STUDIES AND CLINICAL TRIALS

Katie Witkiewitz, University of New Mexico

Individual Abstract: The goal of the current study was to examine the correspondence between levels of alcohol consumption and experiences of drinking-related consequences during and following treatment among individuals receiving treatment for alcohol dependence and in a general population survey. Data from the COMBINE study (n=1383) and NESARC (n=22,245) was used. Across both studies we examined the correspondence between drinking levels (defined as the World Health Organization (WHO) alcohol consumption risk levels) and risk of drinking consequences (COMBINE) or risk of alcohol dependence (NESARC). After controlling for numerous demographic variables and clinical characteristics assessed as baseline, results indicated reductions in WHO risk levels were associated with significantly fewer alcohol related consequences in COMBINE and significantly lower risk of alcohol dependence in NESARC. Importantly, even a one level decrease in WHO risk drinking levels predicted statistically and clinically significant decreases in the risk of experiencing a variety of alcohol related consequences and risk of meeting criteria for alcohol dependence. The reduction in risk of experiencing alcohol related consequences and alcohol dependence was greater for each additional decrease in WHO risk drinking level. The results from the current study provide evidence of reductions in WHO risk levels as a viable alternative to abstinence as an endpoint for alcohol clinical trials. The paper will also discuss the application of WHO risk levels in clinical practice and provide clear guidance for clinicians on the targets for alcohol risk reduction that are most likely to be associated with meaningful reductions in alcohol related consequences.

of special interest to clinicians

Learning Objectives:

- Compare the risk of various drinking consequences and alcohol dependence diagnosis with respect to levels of drinking and the public health implications of consequences at varying levels of drinking in clinical trial and epidemiological data.
- Describe the statistical techniques for examining the associations between consequences and levels of drinking for clinical trial data and epidemiological data.

Literature References:

- Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A: Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 2006; 295:2003–17.
- Moss HB, Chen CM, Yi H-Y: Prospective follow-up of empirically derived Alcohol Dependence subtypes in wave 2 of the National Epidemiologic Survey on Alcohol And Related Conditions (NESARC): recovery status, alcohol use disorders and diagnostic criteria, alcohol consumption behavior. Alcohol. Clin. Exp. Res. 2010; 34:1073–83.

NOVEL EFFICACY ENDPOINTS BASED ON SHIFTS IN THE WORLD HEALTH ORGANIZATION (WHO) RISK LEVELS OF DRINKING: TREATMENT EFFECTS IN ALCOHOL PHARMACOTHERAPY TRIALS

Daniel Falk, NIAAA/NIH

Individual Abstract: Alcohol consumption endpoints are the main efficacy endpoints reported in pharmacotherapy trials to treat alcohol use disorder (AUD). At least a dozen such endpoints, both continuous and dichotomous, have been used in practice. The US Food and Drug Administration currently recommends two dichotomous endpoints for pivotal trials: total abstinence and no heavy drinking (FDA, 2015); however, there may be limitations in their sensitivity to detect the effects of medication for certain trial designs and populations. Thus, there is interest in alcohol treatment community to develop, assess, and validate new dichotomous endpoints that may be more sensitive (i.e., have larger treatment effects), while still being clinically meaningful. The current study evaluated the sensitivity of two relatively novel endpoints that are based on shifts in the World Health Organization (WHO) risk levels of drinking (EMA, 2010) – the percentage of subjects who reduce their risk level by at least 1 and 2 levels. Data were obtained from two multisite alcohol pharmacotherapy trials: 1) the COMBINE study – which evaluated the efficacy of naltrexone (Anton et al., 2006) and 2) the NIAAA Clinical Investigations Group trial of varenicline (Litten et al., 2013). Results from both clinical trials indicated that statistically significant and comparable treatment effects could be obtained using both the WHO 1- and 2-shift endpoints; although a grace period may be required to obtain maximal effects. Moreover, the magnitude of these treatment effects were often as large, or larger, than those obtained by using more traditional continuous and dichotomous endpoints. These findings suggest that the WHO 1- and 2-shift may be worthy of further development as endpoints in alcohol pharmacotherapy trials. Future research should replicate these findings in other multisite trials, as well as validate the clinical utility of risk level shifts against clinically meaningful correlates using a variety of data sources.

Learning Objectives:

- To gain familiarity of the various endpoints used to assess the efficacy of medications in alcohol pharmacotherapy trials.
- To gain an understanding of sensitivity of the new WHO endpoints to detect treatment effects in two alcohol pharmacotherapy trials.

Literature References:

- European Medications Agency (EMA). 2010. Guideline on the development of medicinal products for the treatment of alcohol dependence. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf (accessed November 20, 2015)
- Food and Drug Administration (FDA). 2015. Alcoholism: developing drugs for treatment. Guidance for industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM433618.pdf (accessed November 20, 2015)

USE OF ALCOHOL CONSUMPTION BIOMARKERS IN CLINICAL TRIALS

Raymond Anton, Medical University of South Carolina

Individual Abstract: There is considerable clinical belief, and growing empirical data, that individuals seeking treatment for alcohol use disorders are not always accurate in their reporting of quantity or frequency of alcohol consumption. Some of this is underestimation (willful or unconscious) and some secondary to acute or chronic cognitive impairments associated with drinking. In recent years, several alcohol consumption biomarkers (lab tests) have become more widely available and are being used both in clinical care and in clinical trials to more accurately gauge the success of treatment. There are now three biomarkers of chronic (Serum Carbohydrate Deficient Transferrin - %CDT), sub-acute (Blood Phosphatidyl Ethanol – PEth) and acute (Urinary Ethylglucuronide – EtG) alcohol use that can be applied to clinical investigation and clinical trials. This talk will provide data on their use and how they relate to verbally reported drinking in several NIH funded clinical trials.
Sixty-five alcohol dependent individuals (42M, 23F, 48 y.o.) in an alcohol medication trial were evaluated over 16 weeks with verbal reported drinking by the TLFB calendar method and both %dCDT (MUSC-HLPC method) and PEth (USDTL) were assayed at 6, 10, 16 weeks of treatment. Verbal reports of any or heavy drinking in the month before the blood draw were compared to the %dCDT (>1.7%) and PEth (20ng/ml) positive levels at those time points. Results across the three collection time points in the study were similar. Both %dCDT and PEth give an independent picture of drinking status with PEth being more sensitive to "any drinking" and %dCDT being sensitive to only "heavy drinking". However, when used independently, or in conjunction, it is clear that about 20-30% of individuals who report abstinence or low level drinking during a clinical trial are not accurately reporting their drinking.

Since the FDA draft guidelines suggest those with "no reported heavy drinking days" be considered a success in clinical trials, we also examined how %dCDT (marker of heavy drinking) compared to verbal reported heavy drinking in the final month of a naltrexone clinical trial. Of 118 evaluable people 53% reported no heavy drinking days, when %dCDT positives were considered this number dropped to 38%, suggesting that 15% of people underreport drinking and would be considered good outcomes without %dCDT use.

of special interest to clinicians

In a third clinical trial, urinary EtG was used to confirm abstinence prior to randomization and prior to a brain scanning procedure during the trial. Preliminary data suggest it is useful to detect unreported drinking in both situations.

These data suggest that well-studied and validated biomarkers of alcohol use should be used more widely in clinical trials to provide a more accurate treatment response. They might also be of value in non- alcohol trials (depression, schizophrenia, bipolar etc.) where heavy drinking exclusions need confirmation. This might lead to reduced error variance during efficacy analyses.

Learning Objectives:

- Attendees will be able to recognize the 3 clinically useful biomarkers of alcohol consumption.
- Attendees should recognize the what each alcohol consumption marker measures in the way of drinking levels and understand how they related to reported drinking in clinical trials.

Literature References:

- Litten RZ, Bradley AM, Moss HB. Alcohol biomarkers in applied settings: recent advances and future research opportunities. Alcohol Clin Exp Res. 2010;34:955-967.
- Jatlow PI, Agro A, Wu R, Nadim H, Toll BA, Ralevski E, Nogueira C, Shi J, Dziura JD, Petrakis IL, O'Malley SS. Ethyl Glucuronide and Ethyl Sulfate Assays in Clinical Trials, Interpretation, and Limitations: Results of a Dose Ranging Alcohol Challenge Study and 2 Clinical Trials. Alcohol Clin Exp Res. 2014;38(7):2056–2065.

NOVEL APPROACHES TO TREATMENT-RESISTANT DEPRESSION (TRD)*

Maurizio Fava, Massachusetts General Hospital

Overall Abstract: Major Depressive Disorder (MDD) is a serious, debilitating illness that affects many persons of all ages and backgrounds. All FDA-approved antidepressants used as monotherapies have shown only modest benefits. In fact, in acute (6-8 week) studies, typically with relatively uncomplicated, non-chronic forms of MDD, remission rates range between 30% and 35%. To make matters worse, as currently delivered, none of these pharmacologic and non-pharmacologic treatments have been shown to result in rapid symptom resolution (defined as a sizeable and statistically significant treatment effect versus placebo that is apparent as early as 24 to 72 hours post-initiation of therapy), despite the tremendous need for rapid antidepressant therapies that would allow for meaningful clinical improvements within the context of very short hospital admissions for treatment resistant depression (TRD) patients. The goal of the NIMH-funded RAPID (rapidly acting treatments for major depressive disorder) program is to explore treatments that could meet this need. Furthermore, many pharmacological interventions are associated with significant side-effect burden, leading to the widespread use of nutraceuticals, which are typically tolerated well, despite limited evidence of their efficacy in TRD populations. This panel will review some of the novel approaches to the treatment of TRD. In particular, Dr. Hillefors will review the approach of NIMH to foster rapidly-acting therapies in TRD, while Dr. Fava will present the results from the first of the three NIMH RAPID program studies, focusing on low-field magnetic stimulation. Finally, Drs. Papakostas and Rapaport will review novel leads for future TRD therapies, while Dr. Zarate will serve as the discussant.

Learning Objectives:

- Participants will become familiar with novel pharmacological therapeutical approaches to the treatment of resistant depression.
- Participants will also learn about the use of low-filed magnetic stimulation in the treatment of resistant depression.

THE USE OF ALTERNATIVE AND COMPLEMENTARY THERAPIES IN TRD
Mark Rapaport, Emory University School of Medicine

Individual Abstract: Treatment resistant depression (TRD) is one of the most challenging syndromes to effectively manage in psychiatry. The patients have frequently been tried on a variety of different conventional treatment regiments with no or inadequate response. Many of these patients (and their families) have suffered from intractable depressive symptoms for a long time and most of them have been maintained on complex psychopharmacologic combinations. An increasing number of these patients are resorting to a variety of different complementary and alternative medicine (CAM) approaches either in combination with conventional therapies or in lieu of conventional therapies. The most common type of therapy is the use of some form of natural product. These include agents like omega-3 fatty acids, L-methylfolate, St John's Wort, and s-adenosylmethionine. Unfortunately, the body of both efficacy and safety evidence supporting these approaches is limited and poorly understood. There is an older literature strongly suggesting that a number of non-traditional approaches such as light therapy and sleep deprivation may augment treatment response in patients whose depression is resistant to traditional treatment approaches. These data represent some of the most compelling evidence for efficacy and safety for patients with TRD. However, there is a growing body of evidence supporting the use of a variety of CAM approaches for treating patients with MDD and this work may well offer hope for patients with TRD as well. These intervention strategies include but are not limited to massage, exercise, yoga, acupuncture, and low field magnetic stimulation. The goal of this presentation is to present a critical summary of the state of CAM therapies for mood disorders with special emphasis on their potential application for patients with TRD.

Learning Objectives:

By the end of the presentation the audience will:

- Have an appreciation of the limitations to the current efficacy and safety products commonly employed as augmenting agents or mono therapies for patients with TRD.
- Have an overview of other CAM approaches that should be further studied as augmentation strategies for patients with TRD.

Literature References:

- Ravindran AV, da Silva TL: Complementary and alternative therapies as add-on to pharmacotherapy for mood and anxiety disorders: a systematic review. J Affect Disord. 2013; 150 (3) 707-19.
- Papakostas GI, Shelton RC, Zajecka JM, Bottiglieri T, Roffman J, Cassiello C, Stahl SM, Fava M: Effect of adjuntive L-methylfolate 15 mg among inadequate responders to SSRIs in depressed patients who were stratified by biomarker levels and genotype: results from a randomized trial. J Clin Psychiatry. 2014; 75 (8) 855-63.

NIMH APPROACH TO FOSTERING NEW RAPIDLY ACTING THERAPIES FOR TRD
Mi Hillefors, National Institute of Mental Health

of special interest to clinicians

Individual Abstract: Depression is one of the most common and serious disorders treated by mental health practitioners. While there are a plethora of pharmacologic, psychotherapeutic, and device treatment options available to clinicians, many patients do not respond optimally to the initial treatment offered. Because of the substantial mortality and morbidity associated with inadequate treatment, treatment-resistant depression (TRD) is a major public health concern. To address this problem and foster the development of novel treatments for the TRD, in 2011 NIMH launched the Rapidly-Acting Treatments for Treatment-Resistant Depression (RAPID) initiative. This program seeks to test interventions for TRD that may result in a rapid (<72 hours) therapeutic response. This effort is also expected to lead to enhanced understanding of underlying mechanisms and development of innovative, rapid treatment approaches. Currently three interventions – Low Frequency Magnetic Stimulation (LFMS), a Kappa Opioid Receptor (KOR) Antagonist, and Ketamine – are being evaluated under the RAPID initiative. This presentation will provide an overview of this initiative.

Learning Objectives:

- Panel participants will become familiar with the methodological innovations adopted by the RAPID initiative.
- Panel participants will become familiar with the background and rationale of the RAPID studies on of low-field magnetic stimulation, a kappa opioid receptor antagonist, and ketamine.

Literature References:

- Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CA Jr, Charney DS: Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. Annu Rev Pharmacol Toxicol 2014; 54:119-39
- Rohan ML, Yamamoto RT, Ravichandran CT, Cayetano KR, Morales OG, Olson DP, Vitaliano G, Paul SM, Cohen BM: Rapid mood-elevating effects of low field magnetic stimulation in depression. Biol Psychiatry 2014; 76(3):186-93

LOW-FIELD MAGNETIC STIMULATION IN TRD: THE RAPID STUDY IN TRD

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: After the serendipitous observation of rapid mood improvement during Low Field Magnetic Stimulation (LFMS) in the form of proton echo-planar magnetic resonance spectroscopic imaging (EP-MRSI) of depressed subjects with bipolar disorder, systematic clinical data of such mood changes have been obtained prospectively. LFMS has been reported to rapidly improve mood within minutes of exposure. More specifically, in a study conducted by Rohan et al (Am J Psychiatry 2004), rapid mood improvement was reported by 23 of 30 bipolar disorder subjects who received the actual LFMS in the form of EP-MRSI, by three of 10 bipolar disorder subjects who received sham LFMS, and by four of 14 healthy comparison subjects who received actual LFMS. Significant differences in mood improvement were found between the bipolar disorder subjects who received actual LFMS and those who received sham LFMS, and, among subjects who received actual LFMS, between the healthy subjects and the bipolar disorder subjects and to a lesser extent between the unmedicated bipolar disorder subjects and the bipolar disorder subjects who were taking medication. The electric fields generated by the LFMS scan were smaller (0.7 V/m) than fields used in repetitive transcranial magnetic stimulation (rTMS) treatment of depression (1-

500 V/m) and also extended uniformly throughout the head. A subsequent study by Rohan et al (Biological Psychiatry, 2014) has provided further support for the potential usefulness of LFMS in the treatment of both bipolar and unipolar depression. Substantial improvement (>10% of baseline) in mood was observed following LFMS treatment relative to sham treatment for both diagnostic subgroups for the primary outcomes, the VAS and the HDRS-17. Rapid improvement in mood was also observed using the PANAS scales as secondary measures (positive affect scale p=0.02 BPD, p=0.002 combined group). A finite element method calculation indicated a broad penetration of the LFMS electric field throughout the cerebral cortex. On the bases of these findings, a study by the RAPID Network on LFMS as a treatment of MDD is going to be completed in the first quarter of 2016, using a prototype LFMS device manufactured by Tal Medical. This presentation will review the preclinical and clinical data relevant to the antidepressant efficacy of LFMS, the novel methodologies used in the RAPID study of LFMS, and the results of the RAPID study.

Learning Objectives:

- Participants will become familiar with the preclinical and clinical data suggesting the rapid antidepressant effects of LFMS.
- Participants will also become familiar with the methodology and the results of the RAPID study to assess LFMS efficacy in MDD.

Literature References:

- Rohan M, Parow A, Stoll AL, Demopulos C, Friedman S, Dager S, Hennen J, Cohen BM, Renshaw PF. Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator. Am J Psychiatry. 2004 Jan;161(1):93-8.
- Rohan ML, Yamamoto RT, Ravichandran CT, Cayetano KR, Morales OG, Olson DP, Vitaliano G, Paul SM, Cohen BM. Rapid mood-elevating effects of low field magnetic stimulation in depression. Biol Psychiatry. 2014 Aug 1;76(3):186-93.

NOVEL NON-MONOAMINE-BASED DRUG THERAPIES FOR TRD

George Papakostas, Massachusetts General Hospital

Individual Abstract: Depression is a devastating disorder that places a significant burden on both the individual and society. As such, the discovery of novel therapeutics and innovative treatments-especially for treatment-resistant depression (TRD)-are essential. Research into antidepressant therapies for TRD has evolved from explorations of antidepressants with primary mechanisms of action on the monoaminergic neurotransmitter system to augmentation agents with primary mechanisms both within and outside of the serotonin/norepinephrine system. Now the field of antidepressant research has changed trajectories yet again; this time, compounds with primary mechanisms of action on the glutamatergic, cholinergic, sigma, gaba-ergic, and opioid systems are in the forefront of antidepressant exploration. This talk will review the most recent research surrounding these novel compounds.

Learning Objectives:

- Participants will become familiar with novel non-monoaminergic therapeutical approaches for the treatment of resistant depression.
- Participants will become familiar with additional neurotransmitter systems that, if targeted, may result in novel pharmacological therapeutical approaches for the treatment of resistant depression.

Literature References:

- Papakostas GI, Ionescu DF. Towards new mechanisms: an update on therapeutics for treatment-resistant major depressive disorder. Mol Psychiatry. 2015;20(10):1142-1150.
- Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, Murrough JW. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014;76(12):970-976.

REVISITING EXPERIMENTAL AND CLINICAL THERAPEUTICS OF CANNABIDIOL

Antonio Teixeira, University of Texas Health Science Center at Houston

Overall Abstract: Cannabidiol (CBD) is one of the active phytocannabinoids identified in Cannabis sativa. Experimental studies have demonstrated several psychotropic, anti-oxidant, anti-inflammatory among other effects for CBD. Accordingly, CBD seems to have a wide scope of medical application. The most well-known medical applications of CBD are in epilepsy (Dravet syndrome) and multiple sclerosis related-pain (in association with THC), but there are promising results in other clinical contexts. The objective of the panel is to provide and discuss the current evidence on the potential efficacy of CBD in mood disorders, drug dependence and neurodegenerative diseases.

Learning Objectives:

The panel has two main learning objectives:

- To provide updated information on the pharmacodynamics of CBD.
- To discuss novel potential clinical indications for CBD and cannabinoid receptor agonists/antagonists in neuropsychiatry.

POTENTIAL ROLE OF CANNABIDIOL (CBD) ON THE MOOD DISORDERS THERAPEUTICS

João Luciano de Quevedo, The University of Texas Health Science Center at Houston

Individual Abstract: The endocannabinoid system (ECS), comprising two G protein-coupled receptors (the cannabinoid receptors 1 and 2 [CB1 and CB2] for marijuana's psychoactive principle Δ(9)-tetrahydrocannabinol [Δ(9)-THC]), their endogenous small lipid ligands (namely anandamide [AEA] and 2-arachidonoylglycerol [2-AG], also known as endocannabinoids), and the proteins for endocannabinoid biosynthesis and degradation, has been suggested as a pro-homeostatic and pleiotropic signaling system activated in a time- and tissue-specific way during physiopathological conditions. In the brain activation of this system modulates the release of excitatory and inhibitory neurotransmitters and of cytokines from glial cells. As such, the ECS is strongly involved in neuropsychiatric disorders, particularly in affective disturbances such as anxiety, depression and bipolar disorder. Cannabidiol (CBD), a Cannabis sativa constituent, may present a pharmacological profile similar to anxiolitic, antidepressant and mood stabilizing drugs. The aim of this presentation is to review rodent and human preclinical studies using CBD as an anxiolytic-like, antidepressant-like, and mood stabilizer-like compound and its clinical implications.

Learning Objectives:

- Review the role of the endocannabinoid system (ECS) in the pathophysiology of neuropsychiatric disorders, particularly in affective disturbances such as anxiety, depression and bipolar disorder.

of special interest to clinicians

- Review the rodent and human preclinical studies using CBD as an anxiolytic-like, antidepressant-like, and mood stabilizer-like compound and its clinical implications.

Literature References:

- Bergamaschi MM1, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martín-Santos R, Hallak JE, Zuardi AW, Crippa JA. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology. 2011 May;36(6):1219-26. doi: 10.1038/npp.2011.6. Epub 2011 Feb 9.
- Valvassori SS1, Elias G, de Souza B, Petronilho F, Dal-Pizzol F, Kapczinski F, Trzesniak C, Tumas V, Dursun S, Chagas MH, Hallak JE, Zuardi AW, Quevedo J, Crippa JA. Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania. J Psychopharmacol. 2011 Feb;25(2):274-80. doi: 10.1177/0269881109106925. Epub 2009 Nov 25.

CANNABIDIOL AND ENDOCANNABINOIDS AS POTENTIAL APPROACHES AGAINST COCAINE NEUROTOXICITY

Fabricio Moreira, Federal University of Minas Gerais

Individual Abstract: Cannabidol (CBD), a compound from Cannabis sativa, has been investigated for some therapeutic application in neuropsychiatric disorders. Likewise, synthetic compounds that facilitate the endocannabinoid system may represent new strategies to treat addiction.

Based on previous studies suggesting neuroprotective effects of CBD and endocannabinoids, we have tested the hypothesis that they inhibit the neurotoxic and the abuse-related effects of cocaine in experimental animals.

The methods employed were experimental models of cocaine toxicity in laboratory mice and in cell culture.

CBD inhibited cocaine-induced seizures in experimental animals. It also promoted activation of the PI3K, which is part of an intracellular protective pathway, and prevented cocaine-induced glutamate release in the hippocampus. Moreover, endocannabinoid hydrolysis inhibitors also attenuated cocaine neurotoxicity, though facilitation of CB1 receptor, and prevent the stimulant effects of cocaine, mainly through facilitation of the CB2 receptor.

Altogether, these results indicated that CBD and endocannabinoid hydrolysis inhibitors may contribute to the development of new pharmacological approaches to attenuate the psychostimulant and neurotoxic effects of cocaine.

Learning Objectives:

- To discuss results on the neuroprotective effects of CBD and endocannabinoids against cocaine.
- To discuss the molecular mechanisms underlying the neuroprotective effects of cannabinoids against cocaine.

Literature References:

- Vilela LR, Gobira PH, Viana TG, Medeiros DC, Ferreira-Vieira TH, Doria JG, Rodrigues F, Aguiar DC, Pereira GS, Massessini AR, Ribeiro FM, de Oliveira AC, Moraes MF, Moreira FA. Enhancement of endocannabinoid signaling protects against cocaine-induced neurotoxicity. Toxicol Appl Pharmacol 2015; 286:1781-87.

of special interest to clinicians

- Gobira PH, Vilela LR, Gonçalves BD, Santos RP, de Oliveira AC, Vieira LB, Aguiar DC, Crippa JA, Moreira FA. Cannabidiol, a Cannabis sativa constituent, inhibits cocaine-induced seizures in mice: Possible role of the mTOR pathway and reduction in glutamate release. Neurotoxicology 2015; 50:116-121.

POTENTIAL ROLE OF CANNABIDIOL IN NEURODEGENERATIVE DISEASES

Antonio Teixeira, University of Texas Health Science Center at Houston

Individual Abstract: The endocannabinoid system has emerged as a promising target for the development of neuroprotective strategies. Pre-clinical and clinical evidence support this. For instance, a recent clinical trial performed by our group indicated that CBD (300 mg/day) can improve symptoms and measures of quality of life in Parkinson disease patients.

Learning Objectives:

- To provide pre-clinical evidence on the role played by CBD and other cannabinoids in the pathogenesis of neurodegenerative diseases.
- To discuss the potential therapeutic role for CBD and cannabinoid receptor agonists/antagonists in Parkinson disease and Alzheimer's disease.

Literature References:

- Chagas MH, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM, dos Santos AC, Teixeira AL, Hallak JE, Crippa JA. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol. 2014 Nov;28(11):1088-98.
- Saito VM, Rezende RM, Teixeira AL. Cannabinoid modulation of neuroinflammatory disorders. Curr Neuropharmacol. 2012 Jun;10(2):159-66.

LITHIUM: THE OLD NEW WONDER DRUG*

James Kocsis, New York Presbyterian Hospital

Overall Abstract: Lithium is one of the few medications from the first generation of psychopharmacology to survive and thrive as a first line agent in 2015. Why is that? What is the special value and role of lithium in modern psychopharmacology? This panel will review and discuss targets and methods of lithium therapy. Some are novel such as lithium for suicide prevention and lithium after ketamine. Recent large scale comparative effectiveness studies LITMUS and CHOICE will be summarized. Recent research on genetic markers for bipolar disorder and lithium response will be discussed

Learning Objectives:

- Attendees will learn the current modern day indications and use of lithium in psychiatric disorders and management of long-term risks of lithium therapy.
- Attendees will learn about recent research on genetic markers for bipolar disorder and lithium response.

WHY, WHEN AND HOW DO I PRESCRIBE LITHIUM TODAY?

James Kocsis, New York Presbyterian Hospital

Individual Abstract: This presentation will summarize the current modern day indications and use of lithium in psychiatric disorders, the long-term risks of lithium therapy, the management of long-term risks of lithium therapy and review the relative value and effectiveness of lithium and other modern-day mood stabilizers such as antiepileptic drugs and atypical antipsychotic drugs for bipolar disorder.

Learning Objectives:

- Attendees will learn the current modern day indications and use of lithium in psychiatric disorders.
- Attendees will learn the long-term risks of lithium therapy.
- Attendees will learn management of long-term risks of lithium therapy.

Literature References:

- Castro VM, Roberson AM, McCoy TH, Wiste A, Cagan A, Smoller JW, Rosenbaum JF, Ostacher M, Perlis RH. Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study. Neuropsychopharmacology. 2015 Aug 21. doi: 10.1038/npp.2015.254. [Epub ahead of print]
- Lewitzka U1, Severus E, Bauer R, Ritter P, Müller-Oerlinghausen B, Bauer M. The suicide prevention effect of lithium: more than 20 years of evidence-a narrative review. Int J Bipolar Disord. 2015 Dec;3(1):32. doi: 10.1186/s40345-015-0032-2. Epub 2015 Jul 18.

CAN LITHIUM EXTEND THE ANTIDEPRESSANT EFFECTS OF KETAMINE? A RANDOMIZED CONTROLLED TRIAL

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Background: Major Depressive Disorder (MDD) is a disabling medical illness and current monoaminergic treatments are slow to act and possess only limited efficacy. Recently, the glutamate NMDA receptor antagonist ketamine has demonstrated rapid antidepressant effects in patients with Treatment-Resistant Depression (TRD). The benefit of ketamine, however, is transient (e.g., up to one week following a treatment session). The current project addresses this gap in medical knowledge by testing ketamine plus lithium as a novel strategy to enhance and maintain the response to ketamine. Methods: Patients with TRD receive a single intravenous (IV) infusion of ketamine (0.5 mg/kg) in order to determine initial antidepressant response status. Response status is operationalized as at least a 25% improvement in symptoms 24 hours following the infusion. Responders are then randomized to lithium or placebo under double blind conditions and patients are continued on their treatment assignment for the duration of the study. Patients subsequently receive another three ketamine treatments over a one-week period. Depression severity measured using the MADRS two weeks following the final ketamine treatment represents the primary study outcome. We hypothesize that depressive scores will be improved in the ketamine-lithium group compared to the ketamine-placebo group. We anticipate treating 45 patients over the 3-year project period.

Results: To date, we have screened 40 patients for study eligibility and 25 patients met all inclusion and no exclusion criteria and agreed to participate. All 25 patients underwent the initial ketamine infusion. Eighteen patients responded (72%) and were randomized to lithium or placebo per protocol. MADRS score was significantly decreased 24 hours following ketamine compared to baseline ($t(23)=10.3$, $p<0.001$). 15 patients (83.3%) completed all study assessments and reached the primary study outcome. The study treatments have been well tolerated and no serious adverse events have occurred in the trial.

of special interest to clinicians

Conclusions: Initial safety and compliance data suggest that the treatment interventions are well tolerated and patients are able to adhere to the protocol. As expected, we have observed a rapid antidepressant effect of ketamine within one day of a single treatment in patients with TRD. Assessment of the efficacy of lithium for continuing the antidepressant effect of ketamine will await study completion.

Learning Objectives:

- To understand the potential roles of ketamine and lithium in the treatment of treatment-resistant depression;
- To appreciate the potential biological interactions between ketamine and lithium and would support the hypothesized clinical synergy.

Literature References:

- Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry. 2013; 170: 1134-42.
- Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013; 74: 250-6.

NEURONAL HYPEREXCITABILITY IN A STEM CELL MODEL OF BIPOLAR DISORDER IS REVERSED BY LITHIUM

John Kelsoe, University of California - San Diego

Individual Abstract: Lithium is the oldest and best mood stabilizer for bipolar disorder, and there is a subset of patients who enjoy an excellent response. The goal of this study is to develop a clinical test that might identify these excellent responders and guide treatment. Three excellent lithium responders and three non-responders were selected from those participating in two relapse prevention prospective trials design to assess lithium response for pharmacogenetic studies. Skin biopsies from these 6 and 4 matched controls were reprogrammed to induced pluripotent stem cells and then differentiated to dentate gyrus glutamatergic granule cells. All neurons from bipolar subjects fired action potential at 3x the rate of control cells. This hyperexcitability was rescued by lithium in vitro but only in the neurons that came from clinical responders. This suggest hyperexcitability may be a core defect in bipolar disorder.

Learning Objectives:

- Participants will learn about lithium, its mechanism of action and pharmacogenetic studies.
- The audience will gain an understanding of stem cells and their role in understanding the basic cause of disease.

Literature References:

- Ament, S a., Szelinger, S, Glusman, G, Ashworth, J, Hou, L, Akula, N, Shekhtman, T, Badner, J a., Brunkow, ME, Mauldin, DE, Stittrich, A-B, Rouleau, K, Detera-Wadleigh, SD, Nurnberger, JI, Edenberg, HJ, Gershon, ES, Schork, N, Price, ND, Gelinas, R, Hood, L, Craig, D, McMahon, FJ, Kelsoe, JR, Roach, JC. 2015. Rare variants in neuronal excitability genes influence risk for bipolar disorder. Proc. Natl. Acad. Sci.: 201424958.
- Mertens, J, Wang, Q-W, Kim, Y, Yu, DX, Pham, S, Yang, B, Zheng, Y, Diffenderfer, KE, Zhang, J, Soltani, S, Eames, T, Schafer, ST, Boyer, L, Marchetto, MC,

Nurnberger, JI, Calabrese, JR, Ødegaard, KJ, McCarthy, MJ, Zandi, PP, Alba, M, Nievergelt, CM, Mi, S, Brennand, KJ, Kelsoe, JR, Gage, FH, Yao, J. 2015. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. Nature 527: 95–99

RESULTS OF RECENT PRAGMATIC STUDIES OF LITHIUM IN BIPOLAR DISORDER

Michael E. Thase, Perelman School of Medicine at the University of Pennsylvania

Individual Abstract: Although lithium is by far the best-established mood stabilizer, many practitioners now use it in a second- or third-line position, apparently reserving its use for patients who do not respond to valproate and second generation antipsychotics (SGAs). There is no empirical rationale for such a practice and, by contrast, a strong case can be made for considering lithium salts to be the strategy of first choice for bipolar I disorder on the basis of cost-effectiveness and track record. The continued role of lithium as the foundational treatment for bipolar disorder was examined in two larger scale, pragmatic trials, one known by the acronym LiTMUS, which was funded by the National Institute of Mental Health, and the other known as Bipolar CHOICE, which was funded by the Agency for Healthcare Quality and Research. These studies were performed sequentially by the Bipolar Treatment Network, a collaborative team of investigators working in university affiliated specialty clinics in the United States. Conducted between 2008 and 2013, the findings of LiTMUS and CHOICE underscore the both the effectiveness and tolerability of lithium therapy within the context of designs that permitted treatment as usual with essentially all contemporary pharmacotherapies. In LiTMUS (6 sites; n=283), bipolar patients randomly assigned to receive low-to-moderate doses of lithium therapy had outcomes that were essentially identical to patients who did not receive lithium, despite being significantly less likely (48% vs 63%) to receive SGAs; 18% of patients withdrew from lithium therapy compared to 15% of those who did not receive lithium. In CHOICE (11 sites; n=562), patients were randomly assigned to receive either lithium (mean blood level: 0.6 mEq/L) or the SGA quetiapine (mean dose: 345 mg/day) as the foundation treatment. There were no significant between-group differences on any of the planned effectiveness or safety analyses. A secondary analysis suggested that, contrary to prediction, patients with higher pretreatment mania scores responded better to quetiapine than lithium. The implications of the findings of LiTMUS and CHOICE for current practice, as well as the limitations of these pragmatically designed studies, will be discussed.

Learning Objectives:

By the end of this presentation, the learner will be able to:

- Describe the goals, principal findings, and implications of the LiTMUS study; and
- Describe the goals, principal findings and implications of the Bipolar CHOICE study.

Literature References:

- Nierenberg AA, Friedman ES, Bowden CL, Sylvia LG, Thase ME, Ketter T, Ostacher MJ, Leon AC, Reilly-Harrington N, Iosifescu DV, Pencina M, Severe JB, Calabrese JR. Lithium treatment moderate-dose use study (LiTMUS) for bipolar disorder: a randomized comparative effectiveness trial of optimized personalized treatment with and without lithium. Am J Psychiatry. 2013 Jan;170(1):102-10. doi: 10.1176/appi.ajp.2012.12060751. PMID: 23288387
- Nierenberg AA, Sylvia LG, Leon AC, Reilly-Harrington NA, Shesler LW, McElroy SL, Friedman ES, Thase ME, Shelton RC, Bowden CL, Tohen M, Singh V,

Deckersbach T, Ketter TA, Kocsis JH, McInnis MG, Schoenfeld D, Bobo WV, Calabrese JR; Bipolar CHOICE Study Group.Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE): a pragmatic trial of complex treatment for a complex disorder. Clin Trials. 2014 Feb;11(1):114-27. doi: 10.1177/1740774513512184. Epub 2013 Dec 17. PMID: 24346608

3:30 p.m. - 5:30 p.m.

Wednesday Afternoon Workshops

AN INTEGRATED TECHNOLOGY APPROACH FOR PREVENTING RELAPSE IN RECENTLY HOSPITALIZED SCHIZOPHRENIA PATIENTS

John Kane, The Zucker Hillside Hospital

Overall Abstract: The course of schizophrenia is characterized by relapses and hospitalizations despite treatment with pharmacotherapy and coordinated care with case managers. The first six months after discharge from an inpatient unit are a time of increased risk for re-hospitalization. Cell phone and web-based technologies are being developed to provide evidence-based interventions for patients with schizophrenia. We describe a coordinated effort, called the Health Technology Program, to provide up to four validated technology tools that were integrated into a Relapse Prevention Plan individually tailored for patients by a Health Technology Coach/Case Manager. These interventions included: a smartphone application called FOCUS designed to provide immediate help with troublesome mood, sleep, or psychotic symptoms, social engagement and medication adherence; web-based CBT for residual voices or paranoia; a psycho-educational Daily Support Website including web-based group forums for patients and family, a library of educational resources, 'ask the expert' service, 'frequently asked questions,' and a news feed; and a web-based Prescriber Decision Assistant to elicit patient symptoms and side effects and encourage evidence-based algorithmic psychotropic selection. 461 male and female patients aged 18-60 with schizophrenia-spectrum disorders within six months of hospital discharge were recruited from 10 community sites in eight states and enrolled in this 6-month intervention. 100 patients who met the same inclusion criteria served as a reference group for comparison. We present baseline patient characteristics and early implementation data, as well as patient-reported benefits, barriers and challenges to the use of these technologies. The Workshop format will permit discussion of the challenges involved in developing an integrated program, training community-based case managers to serve as coaches and providing the ongoing supports required for implementation. Discussion will also focus on future directions including scaling of integrated technology interventions to allow wider dissemination.

Learning Objectives:

- Describe the evidence-based technology tools that have been developed to treat patients with schizophrenia-spectrum disorders.
- Identify patient's perceived benefits, barriers and challenges to implementing technological aids in the care of their illness.

IMPROVING CARE AND REDUCING COSTS: BACKGROUND AND RATIONAL

John Kane, The Zucker Hillside Hospital

Individual Abstract: The course of schizophrenia is characterized by relapses and hospitalizations despite treatment with pharmacotherapy. Additional treatment components such as coordinated care with case managers can be helpful, but is not universally available under current reimbursement constraints. The first six months after discharge from an inpatient unit are a time of especially increased risk for re-hospitalization. The project that we are describing grew out of The Center for Medicare and Medicaid's commitment to funding projects with the goals of improving outcomes, reducing costs and training a new cadre of health care workers who would contribute in important ways towards achieving these goals. The availability of new technologies, which can be used to facilitate disease management by patients themselves, as well as caregivers and providers is a major revolution in health care. Cell phone and web-based technologies are being developed to provide evidence-based interventions for patients with schizophrenia. We developed a coordinated effort, called the Health Technology Program, to provide up to four validated technology tools that were integrated into a Relapse Prevention Plan individually tailored for patients by a Health Technology Coach/Case Manager. These interventions included: a smartphone application called FOCUS designed to provide immediate help with troublesome mood, sleep, or psychotic symptoms, social engagement and medication adherence; web-based CBT for residual voices or paranoia; a psycho-educational Daily Support Website including web-based group forums for patients and family, a library of educational resources, 'ask the expert' service, 'frequently asked questions,' and a news feed; and a web-based Prescriber Decision Assistant to elicit patient symptoms and side effects and encourage evidence-based algorithmic psychotropic selection. 461 male and female patients aged 18-60 with schizophrenia-spectrum disorders within six months of hospital discharge were recruited from 10 community sites in eight states and enrolled in this 6-month intervention. 100 patients who met the same inclusion criteria served as a reference group for comparison. We present baseline patient characteristics and early implementation data, as well as patient-reported benefits, barriers and challenges to the use of these technologies. The Workshop format will permit discussion of the challenges involved in developing an integrated program, training community-based case managers to serve as coaches and providing the ongoing supports required for implementation. Discussion will also focus on future directions including scaling of integrated technology interventions to allow wider dissemination.

Learning Objectives:

Participants will be able to:

- Describe the evidence-based technology tools that have been developed to treat patients with schizophrenia-spectrum disorders.
- Describe the role of the Health Technology Coach in crafting individualized relapse prevention plans for patients with schizophrenia.
- Identify patient's perceived benefits, barriers and challenges to implementing technological aids in the care of their illness.

Literature References:

- Steinhubl SR, Muse ED, Topol EJ. Can mobile health technologies transform healthcare? JAMA. 2014; 311(14):1448-1449. doi: 10.1001/jama.2014.1112
- Somaiya, Mansi, et al. "Changes in cost of treating schizophrenia: Comparison of two studies done a decade apart." Psychiatry research 215.3 (2014): 547-553.

COMPONENTS OF THE HEALTH TECHNOLOGY PROGRAM

Delbert Robinson, Hofstra NS-LIJ School of Medicine

Individual Abstract: The Health Technology Program (HTP) is an intervention of 6 months duration designed to prevent relapse and hospitalization for people with schizophrenia or schizoaffective disorder at high risk of hospitalization based upon having recently required a psychiatric hospitalization. Each participant receives an individualized Relapse Prevention Plan. Plan development is guided by a structured manual that includes goal setting, identification of stressors and formulation of strategies to deal with relapse risk. Needs identified in the individual Plan are mapped to supports provided by the technologies available in HTP. HTP includes several technologies; the first technologies usually introduced are the computer decision support system for medication prescription and the FOCUS smartphone application but the order of introduction can be modified based upon participant needs. The technologies available are as follows. 1) FOCUS: This smartphone application uses audio prompts, visual aids and written text to teach coping strategies for managing symptoms, mood, or sleep problems, for dealing with social situations and for encouraging proper medication use. 2) Prescriber Decision Assistant: This computer decision support system uses a measurement-based care approach and is available to prescribers and participants via a secure website. Participants directly enter data on symptoms, side effects, substance use and treatment preferences into the system. Prescribers evaluation of participants is guided by the participant provided self-assessment data. The system then provides recommendations about evidence-based medication strategies that inform joint client-prescriber decision-making about medication treatment. 3) Web delivered CBT for voices or for paranoia: These web-based programs incorporate traditional CBT elements and exercises in an interactive, self-paced format. 4) The Daily Support Family and Client Website: The Daily Support website (DSW) includes web-accessed libraries of educational resources, an 'ask-the-expert' service, a 'frequently asked questions' library, and a news feed. Moderated web forums (one for participants, another for supporters and one for both groups) focus upon discussions of problem solving, stress reduction and socialization. Phone-based DSW supports include 1) help in detecting and managing early warning signs of relapse and 2) medication reminders. HTP staff includes a Technology Case Manager who develops the relapse prevention plan with participants and who supports participants in use of the technologies. The Workshop format will allow for active discussion regarding development of technology tools for specific patient targets and well as design of research to evaluate their use. The HTP used a suite of technology tools that allowed addressing the goal of personalized medicine. Discussion may also address research design challenges raised by this model.

Learning Objectives:

- Workshop attendees will be able to describe the technologies that are part of the Health Technology Program and consider how they might be used in future treatment and research.
- Listeners will be able to describe the role of the HTP Technology Case Manager, how their activities contribute to the use of the HTP technologies and how technology facilitators can be used in future research and treatment programs.

Literature References:

- Gottlieb JD, Romeo KH, Penn DL, Mueser KT, Chiko BP. Web-based cognitive-behavioral therapy for auditory hallucinations in persons with psychosis: a pilot study. Schizophrenia Research. 2013;145(1-3):82-7.
- Rotondi AJ, Anderson CM, Haas GL, Eack SM, Spring MB, Ganguli R, Newhill C, Rosenstock J. Web-based psychoeducational intervention for persons with schizophrenia and their supporters: one-year outcomes. Psychiatric Services. 2010;61(11):1099-105.

of special interest to clinicians

BASELINE CHARACTERISTICS AND INITIAL USAGE DATA FOR RECENTLY HOSPITALIZED SCHIZOPHRENIA PATIENTS USING AN INTEGRATED TECHNOLOGY APPROACH TO PREVENT RELAPSE VS CONTROLS RECEIVING USUAL CARE

Eric Achtyes, Michigan State University College of Human Medicine

Individual Abstract: Cell phone and web-based e-health technologies are being developed to improve access to care and provide evidence-based interventions across broad areas of medicine, including patients with mental illnesses. There have been concerns whether individuals experiencing the positive, negative, and cognitive symptoms of schizophrenia would be able to successfully utilize e-health technologies due to symptom exacerbations as well as side effects from psychotropic medications. A coordinated effort, called the Health Technology Program (HTP), was implemented to provide up to four technology tools designed specifically for patients with schizophrenia and integrated into an individualized Relapse Prevention Plan by a Health Technology Coach/Case Manager. The four technology tools include: a smartphone application for illness management called FOCUS, web-based CBT for residual psychosis, a psycho-educational and therapeutic Daily Support Website (DSW), and a Prescriber Decision Assistant (PDA) to record symptoms and side effects and support evidence-based psychotropic management. Baseline characteristics and early utilization and usability data for each of the four technologies will be presented for 461 male and female patients and 100 controls with schizophrenia-spectrum disorders, age 18-60, who were recruited within two months of hospital discharge at ten community outpatient sites in eight states and enrolled in the 6 month HTP intervention. A 13-item survey was completed by participants at the end of the 6-month study with three questions addressing each of the 4 digital components. If the participant indicated use of a digital component, they were asked to answer two following questions, each on a 3-point ordinal scale, ranging from "very" to "not at all" for each of the four technology components. The first question asked whether the patient was able to use the digital component successfully ("Usability"), the second asked whether the patient found the component helpful in managing their health ("Helpfulness"). The last item measured the overall satisfaction from the program on a 3-point ordinal scale, ranging from "very satisfied" to "somewhat satisfied" to "not satisfied at all".

Learning Objectives:

- Describe the baseline characteristics of recently discharged adult psychiatric outpatients with schizophrenia-spectrum disorders who were given access to novel technologies as part of a relapse prevention plan, compared to controls receiving usual care.
- Learn about the utilization and usability of four e-health technologies developed specifically for patients with schizophrenia: the smartphone application FOCUS to assist illness management, web-based CBT for residual psychosis, a psycho-educational and therapeutic Daily Support Website, and an algorithmic Prescriber Decision Assistant designed to facilitate evidence-based psychotropic selection.

Literature References:

- Ben-Zeev D, Brenner CJ, Begale M, Duffecy J, Mohr DC, Mueser KT: Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. Schizophr Bull 2014; 40:1244-1253

of special interest to clinicians

- Gottlieb JD, Romeo KH, Penn DL, Mueser KT, Chiko BP: Web-based cognitive–behavioral therapy for auditory hallucinations in persons with psychosis: A pilot study. Schizophr Res 2013; 145:82-87

PATIENT EXPERIENCE OF TECHNOLOGY ENHANCED TREATMENT: WHAT THEY LIKED; BARRIERS TO USE AND SKILLS THEY ACQUIRED

Nina Schooler, SUNY Downstate Medical Center

Individual Abstract: The Health Technology Program (HTP) use of computers and smart phones was a novel experience for the schizophrenia patients who participated in the program. Although patients may have had experience with computers and mobile phones, using these devices as part of their treatment was new. Therefore, we wanted to gain an understanding of how they perceived the experience. We were interested in gathering information about which of the components they used, whether they liked being able to use a smart phone and computer as part of treatment, what barriers they experienced and what skills they had acquired that they would be able to use after the six-month program ended. We inquired about which of the HTP technology tools the participant had used and then asked open-ended questions probing about both positive and negative aspects of the experience. Participants were then asked to respond to a series of statements regarding the tools they had used. Statements were grouped under three categories: "things other people have told us they liked about being in the program"; "things that could get in the of using the tools in the program"; and "things that people have told us they have learned and new skills they have gotten from the program that they can use in the future. "Only statements referring to the tools an individual had personally used were assessed.
Statements to be included in the interview were collected from the Health Technology Case Managers based on reports they had from patients they had treated. We included 19 items reflecting positive features of the program, 15 barriers and 10 new skills.

Telephone interviews, conducted by three experienced clinical interviewers, took place immediately after HTP participants had completed their final six-month assessments. The workshop presenter was one of the interviewers. Case managers introduced the interviewer and then left the room. Interviews lasted about 30 to 40 minutes and 35 interviews were completed. Interviews were conducted once the HTP program was well established at the sites.

Examples of responses to open-ended questions and the specific statements will be presented. Discussion will focus on use of telephone interviews with patients with schizophrenia spectrum diagnoses, the advantages and disadvantages of unstructured responses and specific statements, the merits of including both in the same interview and the advantages of offering patients examples of barriers and problems to consider. The discussion will help guide development of future in-depth assessment of patient response to innovative treatment programs.

Learning Objectives:

- Workshop participants will become familiar with the advantages and barriers to use of computer and smart phone aided treatment as perceived by patient participants.
- Workshop participants will learn about future directions in assessing participant experiences in treatment programs.

Literature References:

- Brooke J. SUS-A quick and dirty usability scale. Usability Evaluation in Industry. 1996:189–194
- Gottlieb JD, Romeo KH, Penn DL, Mueser KT. Web-based cognitive–behavioral therapy for auditory hallucinations in persons with psychosis: A pilot study. Schizophrenia Res, 2013: 145(1-3)82-7

MANAGING THE UNIQUE CHALLENGES ASSOCIATED WITH RAPID ACTING ANTIDEPRESSANT TRIALS

Gerard Sanacora, Yale Department of Psychiatry

Overall Abstract: A growing series of relatively small but highly consistent studies provide intriguing evidence that ketamine can produce rapid and robust antidepressant effects, and possibly anti-suicidal effects in patients suffering from treatment-resistant mood disorders. A recent meta-analysis completed by the American Psychiatry Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments found the data from these studies to provide, "compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient." However, the report also provides a strong caveat: "Yet, this enthusiasm should be tempered with the realization that ketamine's clinical trial data, although positive, remain limited and demonstrate only a transient benefit", highlighting the clear need for additional clinical trial work in this area. In addition to ketamine (and its S-isomer), several other novel NMDA receptor-targeting drugs believed to have rapidly acting antidepressant actions have also entered into clinical trials over the past few years. As the results of these initial studies are beginning to readout, we are becoming increasingly aware of some of the unique challenges facing this novel area of clinical trial research. Awareness of the challenges associated with this line of novel research is critical in both interpreting the findings of completed trials and in improving the design of future trials. This workshop will elucidate the various methodological and interpretative challenges that arise in these studies and consider the various strategies to address these issues. A panel of investigators from academia and industry with specific experience and expertise in this area of clinical trial research will present their views on these challenges and offer possible solutions using data from recently completed or ongoing trials as examples. Dr. Holly Lisanby of the NIMH will serve as the discussant to provide her analysis and overview of the workshop.

Learning Objectives:

- To identify unique challenges associated with clinical trials examining the efficacy and safety of putative rapidly acting antidepressant medications.
- To formulate possible solutions to the challenges to improve clinical trial design.

CHALLENGES OF MEASURING RAPID CHANGES IN SUICIDALITY: IMPLICATIONS FOR CLINICAL TRIALS

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Burgeoning research is examining rapidly acting antidepressant and anti-suicidal agents. In particular, ketamine has emerged as a candidate rapidly acting therapeutic for the treatment of suicidal ideation and elevated suicide risk. The current talk will examine results of a recently completed proof of concept clinical trial of ketamine for rapid reduction of suicidal ideation in patients who present with elevated suicide risk across disorders. Specifically, methodological issues related to the measurement of suicidal ideation

and suicide risk will be considered, including challenges related to the type of measurement instrument used, the time-frame assessed, self-report vs clinician administered assessments, and implicit vs explicit measurements.
In the clinical trial, patients were randomized under double-blind conditions to a single infusion of ketamine or midazolam (as an active placebo) in addition to standard of care. Suicidal ideation measured using the Beck Scale for Suicidal Ideation (BSI) 24 hours post-treatment represented the primary outcome. Secondary analyses included the Montgomery-Asberg Depression Rating Scale–Suicidal Ideation (MADRS-SI) score at 24 hours and additional measures beyond the 24-hour time point. The intervention was well tolerated and no dropouts occurred during the primary 7-day assessment period. BSI score was not different between the treatment groups at 24 hours (p=0.32), however a significant difference emerged at 48 hours (p=0.047). MADRS-SI score was lower in the ketamine compared to midazolam group at 24 hours (p=0.05). The treatment effect was no longer significant at the end of the 7-day assessment period. These findings provide preliminary evidence for the efficacy of ketamine for SI and raise methodological issues that will be considered.

Learning Objectives:

- To become familiar with the emerging field of rapidly acting therapeutics for depression and suicide risk.
- To appreciate the special methodological challenges that are encountered in trials designed to test rapidly acting candidate compounds for the treatment of suicide ideation.

Literature References:

- Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med. 2015 Dec;45(16):3571-80.
- Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014 Apr;31(4):335-43.

INTEGRATING HUMAN BIOMARKERS IN TRIALS INVOLVING INTERVENTIONS WITH RAPID ANTIDEPRESSANT AND ANTISUICIDAL EFFECTS

Carlos Zarate, National Institute of Mental Health

Individual Abstract: Mood disorders are among the most disabling and costly of all medical illnesses producing deleterious effects on individuals, family, and society. Even though a number of antidepressant treatments are available for clinical use, many patients still undergo lengthy and multiple medication trials before the right treatments are found. Furthermore, drug development in depression has not produced an antidepressant drug that is clearly superior and mechanistically distinct from existing options. Exploring biomarkers of diagnosis, treatment response, and relapse of depression may facilitate drug discovery. Multimodal approaches including genetics, proteomics/metabolomics, peripheral measures, neuroimaging, neuropsychopharmacological challenge paradigms and clinical predictors could be incorporated into existing trials. A novel approach to developing biomarkers of response would integrate these multiple biomarkers when using interventions with a rapid onset of action (e.g., ketamine, sleep deprivation, neuromodulatory devices). Promising

putative biomarkers identified could then undergo characterization at multiple research sites. These exploratory biomarkers incorporated into rapid antidepressant trials may then be used for a priori stratification in larger multisite controlled studies with the ultimate goal of surrogacy. This alternative translational model for new treatments in neuroscience would facilitate shorter duration studies, improve feasibility, and increase higher compound throughput testing. Challenges in integrating biomarkers into rapid antidepressant trials and interpreting the results will be discussed.

Learning Objectives:

- The participant will understand different study designs using rapid acting interventions.
- The participant will become familiar with challenges on integrating human biomarkers in studies using rapid acting interventions.

Literature References:

- Developing biomarkers in mood disorders research through the use of rapid-acting antidepressants. Niciu MJ, Mathews DC, Nugent AC, Ionescu DF, Furey ML, Richards EM, Machado-Vieira R, Zarate CA Jr. Depress Anxiety. 2014 Apr;31(4):297-307.
- Human biomarkers of rapid antidepressant effects. Zarate CA Jr, Mathews DC, Furey ML. Biol Psychiatry. 2013 Jun 15;73(12):1142-55.

ASSESSMENT OF RAPID IMPROVEMENT OF DEPRESSION: CHALLENGES ACROSS THE AGE SPECTRUM

Jaskaran Singh, Neuroscience TA, Janssen R & D, LLC, Janssen Pharmaceutical Companies of JNJ

Individual Abstract: Major Depression is severe disorder which is projected to be the leading cause of disability in the developed world. It is associated with high mortality from suicide and other causes. There is an urgent need to develop novel therapies for the treatment of depression. Current therapies have significant limitations in efficacy in patients who do not benefit from available treatments. When these therapies are effective, the onset of efficacy may take weeks, which limits their utility under crisis conditions e.g. suicidal intent. Significant progress has been made recently in the understanding of the pathophysiology of depression, and novel drugs have emerged that have the potential to significantly improve depression and reduce its devastating consequences. However, there are no validated objective biomarkers that can be used to demonstrate the efficacy of novel antidepressants, and regulatory agencies rely on established subjective ratings scales. Rating scales for measurement of depression or suicide were developed for assessment over weeks and have limited capabilities of rapid antidepressant effects, especially for antisuicidal effects. Lack of acceptance by regulatory authorities of novel scales created significant hurdles for development of new drugs and has limit the development of novel drugs especially in vulnerable populations e.g. children/adolescents and suicidal patients. Current limitations and progress will be discussed.

Learning Objectives:

- Limitations of some of the current rating scales in assessing improvement in depression, challenges from clinical and regulatory perspective.
- Adaptations of scales and validation of news scales are significant hurdles for novel drug development and calls for academic-industry consortium to overcome these hurdles.

Literature References:

- Sanders L: No new meds: with drug firms in retreat, the pipeline for new psychiatric medications dries up. Sci News 2013; 183:26–29
- Sanacora G, Schatzberg AF: Ketamine: promising path or false prophecy in the development of novel therapeutics for mood disorders? Neuropsychopharmacology 2015; 40:259–267

STUDY DESIGN CHALLENGES IN DEVELOPING RAPID ONSET ANTIDEPRESSANTS

Suresh Durgam, Forest Research Institute, A Subsidiary of Actavis, plc

Individual Abstract: Almost all of the drugs developed for acute treatment Major Depressive Disorder so far have similar designs for pivotal studies. They are either six or eight weeks in duration and the primary end point was change from baseline to end of week 6 or 8. Each of these drugs (e.g. SSRIs or SNRIs) took several weeks to show improvement. Maintenance of efficacy is typically demonstrated in a randomized withdrawal design where patients are stabilized for 16 to 20 weeks in open-label phase and are then randomized to drug or placebo where the primary end point is comparing the time to relapse.
Studies with Ketamine have shown a rapid improvement in depressive symptoms with in one day. There are few compounds in development that are trying to demonstrate efficacy in MDD with a rapid onset of action. There are several challenges in designing studies for rapid onset antidepressants: 1. duration of the study, 2. timing of assessment of the primary end point, 3. what should be the Key secondary endpoint. Once efficacy is established in acute studies, what would be the recommendation for how long the patient should continue the treatment and how frequent the treatment should be given needs to be addressed?

Learning Objectives:

- Recognize the challenges in designing studies for rapid onset antidepressants.
- Study designs that demonstrated efficacy and safety with rapid onset antidepressant are different than those used in SSRIs /SNRIs studies.

Literature References:

- Rickels, K., Athanasiou, M., Robinson, D. S., Gibertini, M., Whalen, H., & Reed, C. R. (2009). Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. The Journal of clinical psychiatry, 70(3), 326-333.
- Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., ... & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of general psychiatry, 63(8), 856-864.

MANAGING PLACEBO RESPONSE AND PATIENT EXPECTATIONS IN CLINICAL TRIALS

Ronald Marcus, Cerecor

Individual Abstract: Patient expectations directly impacts placebo response rates and are a major source of variability and failure in clinical studies in psychiatric and pain conditions for medications that are effective. High placebo rates in psychiatry clinical trials resulting in

"failed" studies are a major impediment in the development of innovative pharmacological therapies. The study design (e.g., number of arms) and the conduct of the clinical trial will significantly affect participant expectations. This workshop will provide examples of placebo response in clinical studies and how to manage patient expectations and bias in designing and conducting clinical trials. Specific examples will be provided and discussed.

Learning Objectives:

- Clinical researchers will better understand how patient expectations impact placebo response rates in clinical studies.
- Clinical researchers will learn how clinical study design and study conduct will influence patient expectations in drug trials.

Literature References:

- Mora MS, Nestoriuc Y, Rief W: Lessons learned from placebo groups in antidepressant trials. Phil. Trans. R. Soc. B 2011; 366:1879–1888
- Krell HV, Leuchter AF, Morgan M, et al. Subject Expectations of Treatment Effectiveness and Outcome of Treatment with an Experimental Antidepressant. J Clin Psychiatry 2004; 65:1174–1179
- Rutherford B, Sneed J, Roose S: Does Study Design Influence Outcome? The Effects of Placebo Control and Treatment Duration in Antidepressant Trials. Psychother Psychosom. 2009; 78(3):172-181

THE HIDDEN TRUTH IN PSYCHIATRIC TRIALS - MEDICATION ADHERENCE IS HIGHLY VARIABLE - PROBLEMS, IMPLICATIONS, AND SOLUTIONS

Daniel Burch, PPD

Overall Abstract: Outline scope of the non-adherence problem: occasional non-adherence acceptable, however systematic or complete non-adherence can lead to issues with signal detection in trials. Also raises the question of including safety data from subjects who have not taken drug and hence have unreliable data in label.

There are novel solutions to this issue e.g. FDA has recently accepted an application for device-drug combo (Proteus and Otsuka) that tracks adherence, Xhale's breathalyzer technology, etc.

Presentation will discuss study design and or enrichment approaches to address this issue e.g. monitoring adherence in screening period and excluding those non-adherent (RAMPUP design).

Statistical approaches: a priori defining adherence and excluding those non-adherent or other methods to account for non-adherence and;

Regulatory questions/challenges/approaches to systematic non-adherence.

Learning Objectives:

- Understand the impact that non-adherence has on contemporary psychiatric trials.
- Understand potential solutions and the trial method as well as regulatory considerations associated with them.

EVIDENCE AND IMPACT OF NON-ADHERENCE

Daniel Burch, PPD

Individual Abstract: The inferential authority of a randomized clinical trial (RCT) depends on many factors including blinding, treatment allocation, and statistical methods. The assumption that medication adherence is nearly perfect is at the heart of the integrity of an RCT and has a profound influence on all the key features that lend inferential authority. It is well accepted that adherence to prescribed medication in the real world is poor ranging from 60 to as low as 10 percent. What is not as well appreciated is that adherence to study medication in trials which feature unsupervised dosing is also poor. The literature is sparse, but what little data is published suggest the non-adherence can be significant enough to cause trial failure. Besides trial failure, non-adherence can result in underestimating effect size, underestimating safety signals, and confusion about appropriate dosing. Addressing the problem of poor adherence to study medication is paramount to correcting the fundamental problems of assay sensitivity, signal detection, and reproducibility in neuropsychiatric clinical trials.

METHODOLOGICAL APPROACHES TO ENHANCING MEDICATION ADHERENCE IN CNS CLINICAL TRIALS

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: The problem of poor adherence in CNS clinical trials is a big challenge to all those involved in drug development. A recent study (McCann et al, J Clin Psychopharmacology, 2015) assessed the extent of nonadherence, by evaluating pharmacokinetic sampling from 1765 subjects receiving active therapy across 8 psychiatric trials conducted between 2001 and 2011. With nonadherence defined as greater than 50% of plasma samples below the limit of quantification for study drug, the percentage of nonadherent subjects ranged from 12.8%to 39.2%. In addition, our group (Tedlow et al, Biol Psychiatry, 1996) has found that there are no significant differences in current and lifetime comorbidity of Axis I disorders, severity of depression, and levels of overall anxiety, problem solving ability, or quality of life among depressed patients who drop-out of an antidepressant trial and depression patients who do not. These findings suggest that such obvious clinical characteristics do not allow for a meaningful enrichment of more compliant patients into clinical trials. On the other hand, a number of enrichment approaches could be used to enhance treatment adherence in clinical trials. For example, one enrichment approach is based on the use of electronic medical data for eligible patients, where the history of adherence to treatment can be evaluated retrospectively, looking at prescription filling behavior and pattern of regular follow-up visits. This approach assumes that adherence in previous trials is predictive of adherence to future trials. Another enrichment approach is based on the evaluation of blood levels of concomitant medicines that the eligible patient is reporting at the time of screening. Discrepancies (e.g., lack of detectable blood levels of an antidepressant in a patient considered for enrollment into an antidepressant augmentation study) would be interpreted as suggesting poorer adherence. Remote, independent, diagnostic and treatment history assessments are also used to enrich CNS clinical trials with patients more likely to adhere to treatment. Similarly, a number of study design approaches can be used to enhance treatment adherence in clinical trials. For example, one could use a sequential parallel comparison design, where eligibility for analyses of stage 2 would include both non-response to placebo treatment in Stage 1 as well as adherence to treatment in Stage 1, adopting any of the methodologies to track adherence prospectively. Another design approach is the use of any methodology to track adherence, while notifying patients of such use, in order to leverage the Hawthorne (observer) effect. Finally, another design approach is

that of utilizing psychosocial interventions such as cognitive behavioral therapy to enhance adherence to the medication treatment. All these enrichment and design approaches to enhance adherence need to be tested empirically in CNS clinical trials, as our field needs to improve our overall success in evaluating the efficacy of new treatments, as non-adherent subjects are fundamentally uninformative and diminish our ability to detect a signal.

Learning Objectives:

- Participants will learn common enrichment approaches to enhance treatment adherence in CNS clinical trials.
- Participants will learn common study design approaches to enhance treatment adherence in CNS clinical trials.

Literature References:

- McCann DJ, Petry NM, Bresell A, Isacsson E, Wilson E, Alexander RC. Medication Nonadherence, "Professional Subjects," and Apparent Placebo Responders: Overlapping Challenges for Medications Development. J Clin Psychopharmacol. 2015 Oct;35(5):566-73.
- Tedlow JR, Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Rosenbaum JF. Are study dropouts different from completers? Biol Psychiatry. 1996 Oct 1;40(7):668-70.

BRIEF OVERVIEW OF TECHNICAL SOLUTIONS

Atul Mahableshwarkar, Takeda Global Research & Development

Individual Abstract: There is increasing recognition of non-compliance with Investigational Medicinal Product in clinical trials. A number of approaches to identifying and managing this problem have emerged. These include software based systems, smart bottles and smart blister packs, cell phone based apps, facial recognition technologies, smart devices etc. This talk will provide a brief overview and discussions of the solutions currently available and their respective advantages and disadvantages.

IS SUICIDAL IDEATION A SYMPTOM OR A SYNDROME?

Steven Targum, Bracket Global

Overall Abstract: The assessment of suicidal ideation and behavior (SIB) is a safety precaution and a target for treatment in health care and a regulatory requirement in clinical trials. Upon closer examination, the identification and expression of suicidal ideation extends far beyond psychiatric or medical disorders and includes socio-economic, environmental, demographic, and cultural conditions as well. Consequently, the meaning and clinical relevance of suicidal ideation must be considered within the context of these multiple contributing factors. Clearly, a single question (e.g., "Have you thought about ending your life?") cannot capture the complexities of these interacting factors or the nuance of the clinical presentation. It is conceivable that even multiple questions, as contained in the currently existing SIB rating instruments may miss the clinical nuance as well.
In this workshop, we will explore the concept of suicidal ideation both narrowly as a single presenting symptom and more broadly as part of a syndrome (or syndromes) in order to gain a better understanding of the meaning behind the SIB measurements we currently employ.

Learning Objectives:

- Recognize the complexity surrounding the assessment of suicidal ideation because of the multiple contributing factors that can affect the clinical meaning of the assessment.
- Explore different models of conceptualizing suicidal ideation and behavior in an effort to better characterize distinctions between different clinical presentations.

SUICIDAL IDEATION: ONE PIECE OF A LARGER PUZZLE

Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Individual Abstract: Suicidal ideation cuts across the nosological spectrum and is also reported in of the general population. While it provides information about suicide, multiple factors above and beyond suicidal ideation contribute to death by suicide. These factors also cut across diagnoses. One-hundred forty-seven individuals with schizophrenia and schizoaffective disorder were assessed at baseline hospitalization and at two years. Comprehensive baseline data from biological (candidate genes, CSF metabolites), psychological (symptoms, aggression/impulsiveness) and social (premorbid adjustment) factors were gathered. During follow-up, symptoms and suicidal ideation and behavior were assessed. Associations found at baseline will be compared and contrasted with factors associated with subsequent suicide attempts. The data will be presented within the context of a stress-diathesis model. Implications for short-term and long-term intervention will be discussed.

Learning Objectives:

- Participants will be able to discuss a model for understanding suicide.
- Attendees will be able to discuss contributors to suicidal ideation and behavior.

Literature References:

- Mann JJ, Waternaux C, Haas, GL, Malone, KM: Toward a Clinical Model of Suicidal Behavior in Psychiatric Patients. Am J Psychiatry 1999; 156:181–189.
- Simon RI & Hales RE (Eds.). The American Psychiatric Publishing Textbook of Suicide Assessment and Management (2nd ed.). Arlington, VA: American Psychiatric Publishing, 2012.

THERE ARE SEVERAL SUICIDALITY DISORDERS

David Sheehan, University of South Florida College of Medicine

Individual Abstract: Suicidality is orthogonal to depression. In order to search for and investigate candidate anti-suicidality medications we need dimensional rating scales sensitive in detecting the efficacy signal and we need a classification of suicidality disorder phenotypes. Different suicidality disorder phenotypes have a different response to treatment. In those with major depressive disorder (MDD) over 65 years antidepressants are superior to placebo. In those under 25 with MDD, antidepressants worsen suicidality compared to placebo. Clozapine helps reduce suicidality in schizophrenia, while lithium helps reduce suicidality in bipolar disorder. Not all patients with suicidality respond to any of these treatments. This suggests that there may be several suicidality phenotypes and / or genotypes with different responses to treatment. If we put all patients with suicidality into one study with an anti-suicidality medication it is likely to fail, just as any SSRI or SNRI would not separate from placebo if we put all subjects with depressive symptoms into the same trail, without making distinctions between the bipolar depression and the major depressive disorder

phenotypes. We cannot wait until we fully understand the pathophysiology of suicide before seeking and investigating effective pharmacological anti-suicidal treatments. One path forward in pursuit of this goal is to formulate as best we can an interim phenotypic classification of suicidality disorders and concurrently collect investigate genetic biomarkers, while we investigate the response of each to medication treatments. This presentation will offer one possible classification of suicidality disorder phenotypes as a starting point.

Learning Objectives:

- Appreciate and to evaluate the evidence suggesting that suicidality is more a collection of different primary disorder phenotypes than a symptom complicating depression.
- Have a working model of a classification for suicidality disorders, with related diagnostic criteria and associated structured diagnostic interview.

Literature References:

- Sheehan DV Giddens JM. Chapter 6: A Classification of Suicidality Disorders in Suicidality: A Roadmap for Assessment and Treatment. Harm Research Press. Tampa, FL, USA. 2015.
- United Nations. Best Practice Guidelines for Developing International Statistical Classifications. UN Department of Economic and Social Affairs Statistics Division. Report from Expert Group Meeting on International Statistical Classifications. New York, NY: May 13–15, 2013.

CHARACTERIZATION OF SUICIDE IDEATION IN DEPRESSED PATIENTS IDENTIFIED TO BE AT RISK FOR SUICIDE AND KETAMINE TREATMENT RESPONSE

Larry Alphs, Janssen

Individual Abstract: Purpose: The purpose of this presentation will be to characterize suicide ideation in a group of patients with Major Depressive Disorder who have been identified to be at imminent risk of suicide. This characterization will be based on descriptions of suicidal ideation permitted by a newly developed Suicide Ideation and Behavior Assessment Tool (SIBAT).

Content: Major depressive disorder (MDD) is associated with a risk of suicide that is about 20 times that of the general population. Symptoms of suicide in this population can be characterized with the SIBAT according to a number of mediating and moderating phenotypic and demographic characteristics, including age, gender, substance use, history of childhood trauma, etc. It remains unclear if there are any patterns among these characteristics that might be clinically meaningful to treatment outcomes.

Methodology: To characterize suicide symptoms in this population, baseline data on the SIBAT from an ongoing 12-week, randomized, double-blind (DB), placebo-controlled, multicenter study of intranasal esketamine in 70 adults with MDD will be examined. Eligible subjects must have had active suicidal ideation and intent, and have been in need of psychiatric hospitalization. The SIBAT provides a patient-completed structured approach to characterization of suicide ideation (SI) and assessment of suicide risk. This approach provides consistency in evaluating potentially suicidal patients along multiple dimensions of risk and protective factors identified from 5 separate modules of the SIBAT. If patterns can be identified, these symptom clusters will be examined by ordinal mediation analysis to examine relationship of these phenotypic groupings to ketamine treatment response.

of special interest to clinicians

Results: The esketamine study in patients with active suicidal ideation is ongoing in the United States with nearly all subjects enrolled. All baseline data will be analyzed for phenotypic clustering. Optimal description of the data from the SIBAT descriptions of suicide ideation will be identified. The structure so identified will be used to examine differential treatment response to esketamine.

Importance to Field: There remains considerable debate within the field of suicidology regarding the presence of any substructure of symptoms in persons with SI. This work will provide evidence for such structure using the newly developed SIBAT. It will then evaluate whether any substructure so identified bears relationship to treatment response to ketamine.

Learning Objectives:

- To provide initial evidence of substructure among suicidal ideation phenotypes.
- To provide initial evidence regarding whether this substructure might affect treatment response to ketamine.

Literature References:

- Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, Brutsché NE, Ameli R, Furey ML, Zarate CA Jr, Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. 2014 Nov; 58:161-6. doi: 10.1016/j.jpsychires.2014.07.027. Epub 2014 Aug 12.
- Alphs L, Anand R, Islam MZ, Meltzer HY, Kane JM, Krishnan R, Green AI, Potkin S, Chouinard G, Lindenmayer JP, Kerwin R. The international suicide prevention trial (interSePT): rationale and design of a trial comparing the relative ability of clozapine and olanzapine to reduce suicidal behavior in schizophrenia and schizoaffective patients; Schizophr Bull. 2004; 30(3):577-86.

Thursday, June 2, 2016

8:15 a.m. – 9:45 a.m.

Keynote/Plenary

BEYOND SINGLE MAGIC BULLETS: TRUE INNOVATION IN NEUROPSYCHIATRIC CONDITIONS

Husseini Manji, Janssen Research & Development, LLC

Overall Abstract: Worldwide, neuropsychiatric diseases are some of the most debilitating and disabling medical conditions. In addition, because of demographic trends and the lack of effective treatments to modify disease course, the economic and societal burden of these disorders are projected to increase in the coming years. These diseases are caused by dysregulations that span genetic, epigenetic, proteomic, and brain circuitry (connectomics) networks, and they affect complex phenotypes, including memory, cognition, emotion, function, and behavior. Effectively addressing such complex, multi-scale, multi-level disorders will necessarily require multi-pronged interventions that go 'beyond the pill' and use newly-developed advances in mobile computing, devices, and computer-based therapies to intercept these diseases in their earliest stages, when they still modifiable, and before irreversible damage has occurred.

Psychiatric diseases are chronic diseases of the young, in that they often take hold in late adolescence/early adulthood and have a subsequent dynamic course characterized by relapses and recurrences of increasing frequency. Each episode of illness inflicts considerable trauma to patients and caregivers, as well as considerable cost to the healthcare system. For example, patients with schizophrenia and a recent history of relapse generate direct medical costs that are three- to five-fold higher than other medical disorders; relapses are also disproportionately associated with negative outcomes such as higher prevalence of substance use disorders and worsening functional status. Furthermore, recent neuroimaging studies have revealed that relapses and recurrences are not just symptomatic exacerbations of the illness, but actually may cause irreversible atrophic changes in the brain that represent progression of underlying neuropathology. As a result, there is a strong imperative to move from reactive treatment of relapses and recurrences to a more proactive regimen of prediction and preemption. Significant technological advances have been made, particularly with regard to methods capable of remotely capturing rich phenotypic information from streamed data drawn from wearable devices over prolonged observation periods. Such advances provide new ways to monitor long-term outcomes and, via real-time analysis of data streams, to remotely detect changes in clinical status. The reliable identification of such changes and biosignatures will fundamentally re-engineer health care systems to provide more precise care and interventions early in the course of relapse/deterioration, or even before clinical changes are apparent. It should be noted that, while predicting and preempting relapse has immense value, intercepting these diseases in their prodromal stages—prior to conversion to clinical diagnosis—should remain the ultimate goal. This is particularly true of diseases like Alzheimer's disease wherein overt clinical symptoms typically appear almost a decade before the onset of pathology. Interestingly, computer-based cognitive tests have the potential to convert cognition from a subjective and noisy endpoint to a sensitive and quantitative biomarker that will facilitate early detection of Alzheimer's disease and aid the development of sensitive efficacy endpoints for early AD clinical trials. In the future, more sensitive measures of functional decline based on wearable technology and data from smart homes and devices ('internet of things') will help us track disease course and develop customized interventions (cognitive prosthetics) that increase independence and improve quality of life for Alzheimer's patients.

Finally, increasing our understanding of the role that dysfunction in circuit dynamics and synaptic plasticity play as causal drivers of cognitive impairment and psychiatric disorders will lead to increased use of device- and computer-based interventions. Indeed, the most effective therapeutic combinations may well be those that meld pharmacological and non-pharmacological approaches to simultaneously target molecular pathology and brain circuitry.

In this session, the speaker will explore—via specific examples—how novel technologies can be harnessed to develop integrated solutions that will help us move from a 'diagnose and treat' to a 'predict and preempt' paradigm, with the ultimate goal of modifying disease course and improving patient outcomes.

DATA AND INFORMATICS CHALLENGES IN MOVING FROM A 'DIAGNOSE AND TREAT' TO A 'PREDICT AND PREEMPT' PARADIGM

Vaibhav Narayan, Johnson & Johnson

of special interest to clinicians

Individual Abstract: Neurodegenerative and psychiatric disorders are usually characterized by a prolonged asymptomatic phase that precedes appearance of overt symptoms. Successful intervention in these early stages requires characterization of the prodrome with regards to genetic risk and dysregulation in upstream pathways that drive disease pathophysiology. Early disease interception would require data-driven biosignatures of prodromal disease states, sensitive measures of disease state and treatment efficacy, predictive models of disease progression and a clearer understanding of disease subtypes that can be mechanistically targeted with novel therapies. Current models of prodromal stages of diseases like Alzheimer's, depression and schizophrenia are largely based on phenomenology and lack specificity or predictive value. Detailed characterization of prodromal populations via dense longitudinal phenotyping that incorporate environmental factors as well as molecular and neuroimaging readouts are required to identify at-risk populations and build prognostic models of conversion to clinically manifest disease. Knowledge of disease subtypes will enable identification of subpopulations that are not likely to respond to current therapies, and thus reduce the time between identification of prodromal illness and treatment with a novel interception therapeutic. In general, a more comprehensive approach that establishes a network of solutions related to diagnosis, predictive modeling of disease trajectory, efficacy monitoring, and adherence tools would be required to enable discovery, development, and clinical adoption of early interception therapies. This would require integration of data across long time-spans from predisease states to long-term efficacy and outcome data in established chronic diseases. Currently such data are collected by different entities and organizations and is often fragmented and siloed. For example, controlled-trials drug-efficacy data are largely the realm of pharmaceutical companies. Follow-on data on clinical care and outcomes are managed by hospital systems and health insurance companies. Data related to wellness and natural aging are less prevalent and even more fragmented. Going forward, we expect that increasing amounts of longitudinal data ranging from base-line genetics to late-stage disease outcomes will increasingly be owned and controlled by the patients themselves, while being made available to the healthcare system at large. As a new data ecosystem evolves, a robust framework related to data sharing, privacy and ownership will be required, if we are to realize the goal of early identification and interception of disease. In this talk we will explore, via specific examples, how some of these data related challenges may be addressed to hasten the transition from a 'diagnose and treat' to a 'predict and preempt' paradigm.

SENSING BEHAVIORAL SYMPTOMS OF MENTAL HEALTH AND DELIVERING PERSONALIZED INTERVENTIONS USING MOBILE AND WEARABLE TECHNOLOGIES

Tanzeem Choudhury, Cornell University

Individual Abstract: Mobile and ubiquitous computing research has led to new techniques for cheaply, accurately, and continuously collecting data on human behavior that include detailed measurements of physical activities, social interactions and conversations, affect, as well sleep quality and duration. Continuous and unobtrusive sensing of social and physical functioning has tremendous potential to support the lifelong management of mental illnesses by: (1) acting as an early warning system to detect changes in mental well-being, (2) delivering context-aware, personalized micro-interventions to patients when and where they need them, and (3) by significantly accelerating patient understanding of their illness. These unique properties of mobile and ubiquitous computing seem particularly well suited for the management of mental health.

of special interest to clinicians

Developing effective health-care interventions is a complex task. Like any medical intervention, the successful introduction of mobile sensing technologies into mental health care needs to address factors related to patient and clinician acceptance. In order for passive sensing to have a major impact on serious mental illness, technologists need to bring a consideration of patients and their clinicians to bear on system development. This includes: providing individuals with control, being sensitive to the ways information is shown to the user, and recording only as much information as is needed to support clinical decision-making and privacy. Technologists are only beginning to address the challenges associated with striking the right balance between cutting-edge technology and patient needs. In this presentation, I will give an overview of our work on turning sensor-enabled mobile phones into well-being monitors and instruments for administering real-time/real-place interventions. I will also describe our efforts to develop strategies that strike a balance between the potential for ubiquitous sensing and user acceptance.

IMPROVING BRAIN HEALTH AND TRAJECTORIES AND OUTCOMES FOR NEUROPSYCHIATRIC DISORDERS USING TECHNOLOGIES
Barbara Sahakian, University of Cambridge

Individual Abstract: While many people monitor their physical health using mobile devices and wearable technology to preserve their physical health throughout their life course, they rarely consider improving and monitoring their brain health. This is strange, when we consider the regrettable statistics that one in four of us will suffer a mental health disorder at some point in our lives and that 75% of mental health disorders start before 24 years of age and 50% before 18 years of age. If we are going to have good mental capital and wellbeing throughout our lives, it is imperative that we consider mental health as being every bit as important as physical health and move to game- changing initiatives which includes early detection and early effective treatment of neuropsychiatric disorders (Narayan and Manji 2016; Beddington et al 2008; Sahakian 2014). Major approaches will include biomarkers, including cognitive ones, for early detection, but also will utilise novel pharmacological and also technological approaches to treatment, including neuroprotective drugs for Alzheimer's disease, fast acting antidepressant drugs for depression, cognitive enhancing drugs and game apps for delivering cognitive training on mobile phones or tablets in schizophrenia and other neuropsychiatric disorders (Sahakian et al 2015; National Academies of Sciences Engineering and Medicine 2015; Insel et al 2013; Bruhl and Sahakian 2016). In changing the framework by moving to early detection and early effective treatment, we can stop these mental health disorders becoming debilitating, chronic and relapsing. Using these novel pharmacological and non-pharmacological treatment approaches, we can ensure that patients with neuropsychiatric disorders have better quality of life, functionality and wellbeing. Not only can innovation and technology promote a flourishing society, but could also reduce the cost and burden of neuropsychiatric disorders for governments.

10:00 a.m. – 12:00 p.m.

NIH Institute Directors Plenary

NIH INSTITUTE DIRECTORS
Michael E. Thase, Perelman School of Medicine at the University of Pennsylvania

of special interest to clinicians

Overall Abstract: This year's Institute Director's Plenary session will bring together directors from various NIH institutes who all have a similar goal of searching for new approaches in the research of brain and behavior disorders. Each director will have ten minutes to discuss the current initiatives within their institute. George Koob, representing NIAAA, will discuss what science can tell us about the Diagnosis, Prevention, and Treatment of Alcoholism. Amir Tamiz, representing NINDS, will cover initiatives and programs that support the design, implementation, and management of research activities for critical translational challenges in neurology. Chris Austin, representing NCATS, will discuss an overview of NCATS' progress in pre-clinical drug development, new strategies for safety and efficacy, and efforts to create a coherent national network in clinical translation. Ivan Montoya, representing NIDA, will provide an overview of the current opioid use epidemic and an update of NIDA-supported research on new therapeutic options for opioid addiction and overdose. Richard Nakamura, representing CSR, will discuss the current status of the review of NIH grant applications with special emphasis on the review of rigot and transparency. Sarah Lisanby, representing NIMH, will highlight new initiatives that promise to change how we study and treat psychiatric disorders through the transdiagnostic approach to domains of function, the BRAIN Initiative, experimental medicine approach to trial design, and the importance of new developments in data science.

WHAT SCIENCE CAN TELL US ABOUT THE DIAGNOSIS, PREVENTION, AND TREATMENT OF ALCOHOLISM

George Koob, National Institute on Alcohol Abuse & Alcoholism

Individual Abstract: Alcohol use disorders cause an enormous amount of human suffering, loss of productivity and cost to our medical care system and the nation's economy. Advances in the neuroscience of alcohol use disorders can lead the way to better diagnosis, treatment and prevention of this significant public health problem. Conceptualizing alcoholism from an allostatic perspective with a binge/intoxication stage, a withdrawal/negative affect stage, and a pre-occupation/anticipation (craving) stage has allowed identification of key neurocircuits that underlie addiction to alcohol. Such a knowledge base provides the heuristic framework for the development of novel, science-based approaches to diagnosis, prevention and treatment of alcohol use disorders, including medication development, and will facilitate the implementation evidence-based practice in primary care, mental health, and other health care settings.

NINDS UPDATE

Amir Tamiz, NINDS Office of Translational Research

Individual Abstract: Dr. Tamiz will cover NINDS research priorities and funding opportunities to support translational and clinical neuroscience research. The presentation will cover initiatives and programs that support the design, implementation, and management of research activities for critical translational challenges in neurology.

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES UPDATE

Christopher Austin, National Institutes of Health, National Center for Advancing Translational Sciences

Individual Abstract: To meet the opportunities and needs in translational science, NCATS focuses on what is common to diseases and the translational process, and acts a catalyst to bring together the collaborative teams necessary to develop new technologies and paradigms to improve the efficiency and effectiveness of the translational process, from target validation through intervention development to demonstration of public health impact. This update will provide an overview of NCATS' progress in pre-clinical drug development, new strategies for safety and efficacy, and efforts to create a coherent national network in clinical translation.

NIDA UPDATE
Ivan Montoya, DHHS/National Institute on Drug Abuse

Individual Abstract: In recent years, the country has been facing an epidemic of opioid use. For example, heroin use has doubled and prescription of oxycodone and hydrocodone have almost tripled. In 2014, there were almost 19,000 deaths due to opioid overdose and most of them (14,000) were due to prescription opioid overdose. Multiple efforts are being devoted to the prevention and treatment of opioid addiction and overdose. They include the development of new medications and biologics to treat these clinical challenges. Ivan Montoya, representing NIDA, will provide an overview of the current opioid use epidemic and an update of NIDA-supported research on new therapeutic for opioid addiction and overdose.

THE CENTER FOR SCIENTIFIC REVIEW OF NIH – CHANGES COMING
Richard Nakamura, NIH/NIMH

Individual Abstract: Current status of review of NIH grant applications with be discussed. Special emphasis with be placed on the review of rigor and transparency, including sex as a biological variable and resource authentication.

NIMH UPDATE
Sarah Lisanby, NIH/NIMH

Individual Abstract: Despite considerable advances in neuroscientific understanding of brain-behavior relationships and the biopsychosocial contributors to mental illness, the degree of disability and morality arising from psychiatric illness remain unacceptably high. Recognizing the need to bend the curve to improve public mental health, and the important role that mental health plays in overall physical health, the NIMH has embarked on a number of new initiatives that seek to transform our approach to diagnostics, therapeutics, and knowledge generation. Dr. Lisanby's presentation will highlight new initiatives that promise to fundamentally change how we study and treat psychiatric disorders through the transdiagnostic approach to domains of function, the BRAIN Initiative, experimental medicine approach to trial design, and the importance of new developments in data science.

2:00 p.m. - 3:30 p.m.

PSYCHOPHARMACOLOGY STATE-OF-THE-ART UPDATES

of special interest to clinicians

Holly Swartz, University of Pittsburgh School of Medicine

Overall Abstract: The purpose of this symposium is to provide an overview of the recent advances in clinical psychopharmacology leading to the development of novel treatments for mood disorders. This session will focus on the following topics:

- Terence Ketter will discuss advances in treatments for Bipolar Disorder.
- Barbara Mason will discuss the evidence base for FDA-approved medications to treat alcohol use disorder, including potential differential treatment effects for males and females.
- Mark Rapaport will provide updates on complementary and alternative approaches to treating mood and anxiety disorders.

BIPOLAR DISORDER TREATMENT UPDATE, 2016

Terence Ketter, Stanford University School of Medicine

Individual Abstract: There have been several substantive advances since the ASCP 2014 Annual Meeting Bipolar Disorder Treatment Update. New FDA-approvals include: (1) olanzapine plus fluoxetine for pediatric (age 10-17 years) acute bipolar I depression; (2) asenapine monotherapy for pediatric (age 10-17 years) acute mania; and (3) cariprazine monotherapy for adult acute mania. In addition, a 28-week, multicenter, randomized controlled trial indicated lurasidone adjunctive therapy (added to lithium or valproate) in bipolar I disorder was generally safe/well-tolerated and delayed any mood episode recurrence after index depressive (but not mood elevation) episodes, as well as depressive (but not mood elevation) episodes after any index mood episode. Uncontrolled longer-term (16- to 26-week) trials in adult bipolar I disorder patients indicated that longer-term treatment with: (1) armodafinil adjunctive therapy (added to bipolar maintenance treatments); (2) asenapine monotherapy; (3) cariprazine montherapy; (4) lurasidone monotherapy; and (5) lurasidone adjunctive therapy (added to lithium or valproate) yielded differential safety/tolerability profiles.

ALCOHOL USE DISORDERS

Barbara Mason, The Scripps Research Institute

Individual Abstract: The evidence base for FDA-approved medications to treat alcohol use disorder (naltrexone and acamprosate) will be reviewed, including potential differential treatment effects for males and females. Medications in the pipeline for development as new treatments for alcohol use disorder will also be discussed. Finally, the efficacy of psychiatric medications for patients with alcohol use disorder, with and without psychiatric comorbidity, will be summarized.

COMPLEMENTARY AND ALTERNATIVE APPROACHES TO MOOD AND ANXIETY DISORDERS

Mark Rapaport, Emory University School of Medicine

Individual Abstract: I will use our own research investigating natural products and massage therapy to highlight both the state of the field with regard to mood and anxiety disorders as well as some of the challenges investigators face.

3:45 p.m. - 5:45 p.m.

Thursday Afternoon Workshops*

IMPLEMENTATION OF UNIVERSAL DEPRESSION SCREENING AND MEASUREMENT BASED CARE IN BUSY CLINICAL PRACTICES: LESSONS LEARNED FROM PROJECT VITALSIGN6

Manish Jha, UT Southwestern

Overall Abstract: Most patients with major depressive disorder (MDD), especially minority and with low-income, either go undiagnosed or untreated. Primary care providers, who can treat depression initially with outcomes similar to those as psychiatrists, should implement universal depression screening and MBC in patients who screen positive. Barriers to these implementations include persistent stigma of depression, lack of time in high-volume clinical practices, and shortage of behavioral health services for difficult to manage patients. At UT Southwestern, we have developed partnerships with primary care clinics which predominantly serve minority and low-income population and have widely implemented routine depression screening and MBC in patients who screen positive. Over the last year, using this program, we have screened over 14,000 patients in primary care clinics and identified over 1000 previously undiagnosed depressed patients who now receive measurement based care from their primary care providers.

This workshop will start with presentations on how to develop partnerships with providers in the community to implement universal screening of depression and MBC and will detail our process of seamless integration of a quality improvement project in high-volume busy clinical practices. The presenters will then discuss the important elements of MBC tools and how these standardized tools can be administered using point-of-care innovative software loaded on mobile computing devices such as tablets and laptops. The presentations will be followed by hand-on workshop where workshop participants will be divided in three to six small groups. Using multiple training devices (iPads), workshop faculty will demonstrate the VitalSign6 application developed at UT Southwestern which is currently being used to universally screen all patients for depression in partnering clinics, tracking symptoms over time positive screens, and assist the clinicians in delivering MBC of depression and anxiety. In these small groups, participants will be led through a discussion of the anticipated challenges of implementing such an evidence-based intervention in their settings or communities, the practice redesign involved in adoption of these interventions, the barriers to translation to the "real world", and how they plan to implement MBC in their practice.

Learning Objectives:

- Understand the importance of universal screening of depression and routine implementation of measurement based care (MBC) to attain functional recovery in depressed patients.
- Identify the opportunities to use health IT tools like point-of-care software programs to administer self-report instruments and formulate a plan to implement MBC in their practice.

MAKING EVIDENCE-BASED TREATMENT OF DEPRESSION EASILY ACCESSIBLE: FORGING COLLABORATIONS WITH PRIMARY CARE CLINICS

Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: Due to the severe shortage of psychiatric providers in the United States, most of the burden of screening, diagnosis, treatment, and follow-up of depression have been thrust onto other medical providers. Unfortunately, half of the depressed patients seen in medical settings will not be recognized as suffering from depression. For those actually treated with antidepressants, only one out of five patients receive adequate treatment. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated that primary care providers can treat depression initially with outcomes similar to those as psychiatrists, and supports the implementation of universal depression screening and measurement based care in patients who screen positive. Barriers to these implementations include persistent stigma of depression, lack of time in high-volume clinical practices, and shortage of behavioral health services for difficult to manage patients. At UT Southwestern, we have developed partnerships with primary care clinics which predominantly serve minority and low-income population and have widely implemented routine depression screening and MBC in patients who screen positive. Over the last year, using this program, we have screened over 22,000 patients in primary care practices and identified over 2500 previously undiagnosed depressed patients who now receive measurement based care from their primary care providers. Workshop participants will learn about how to develop partnerships with providers in the community to implement universal screening of depression and measurement based care, and will detail our process of seamless integration of a quality improvement project in high-volume busy clinical practices.

Learning Objectives:

- Understand the importance of universal screening of depression and routine implementation of measurement based care (MBC) to attain functional recovery in depressed patients.
- Identify the opportunities to use health IT tools like point-of-care software programs to administer self-report instruments and formulate a plan to implement MBC in their practice.

Literature References:

- Kessler, R.C., et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama, 2003. 289(23): p. 3095-105.
- Trivedi, M.H., et al., Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry, 2006. 163(1): p. 28-40.

ENHANCING MEASUREMENT BASED CARE: WHY DOES FUNCTIONAL RECOVERY MATTER?

Tracy Greer, University of Texas Southwestern Medical Center at Dallas

Individual Abstract: The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that it is possible to provide high quality treatment in primary care settings with outcomes equal to those provided by specialty care using Measurement Based Care (MBC). The important elements of MBC, which have been adopted in treatment

guidelines for depression, are standardized assessments of symptoms, side-effects and adherence, multi-step decision making for treatment, consistent follow-up, and feedback to assist clinical decision making. However, symptom severity reflects only a portion of the burden of Major Depressive Disorder (MDD). Functional impairments often persist after symptomatic remission, are associated with worse long-term clinical outcomes, and are of great importance to patients. Functional recovery is distinct from symptomatic recovery, and therefore assessments geared to evaluate changes in function and quality of life can enhance the quality of clinical care. Workshop participants will learn to integrate standardized self-report functional assessments that can inform future clinical decisions.

Learning Objectives:

- Understand the importance of universal screening of depression and routine implementation of measurement based care (MBC) to attain functional recovery in depressed patients.
- Identify the opportunities to use health IT tools like point-of-care software programs to administer self-report instruments and formulate a plan to implement MBC in their practice.

Literature References:

- Kessler, R.C., et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama, 2003. 289(23): p. 3095-105.
- Trivedi, M.H., et al., Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry, 2006. 163(1): p. 28-40.

HARNESSING HEALTH INFORMATION TECHNOLOGY TO IMPLEMENT MEASUREMENT BASED CARE: DEMONSTRATION OF VITALSIGN6 SOFTWARE

Manish Jha, UT Southwestern

Individual Abstract: Routine screening of depression in a clinical practice can be expedited by the use of validated screening tools such as the 2-item Patient Health Questionnaire (PHQ-2). However, after a positive screen, implementation of measurement based care (MBC) is typically limited by factors such as shortage of time and reliance on clinicians to monitor symptoms, dose titration, adherence, and side effects. The VitalSign6 software is a point-of-care, web-based application designed to screen patients for depression, monitor symptoms over time for those patients who screen positive, and guide providers in treatment planning and decision making. Workshop participants will watch a demonstration of the VitalSign6 software, developed at UT Southwestern, which is currently being used to screen all patients for depression in partnering community-based clinics, to track symptoms over time in patients with positive screens, and to assist clinicians in delivering MBC of depression and anxiety. After the demonstration, participants will be led through a discussion of the anticipated challenges of implementing such an evidence-based intervention in their settings or communities, the practice redesign involved in adoption of these interventions, the barriers to translation to the "real world", and how they plan to implement MBC in their practice.

Learning Objectives:

- Understand the importance of universal screening of depression and routine implementation of measurement based care (MBC) to attain functional recovery in depressed patients.

- Identify the opportunities to use health IT tools like point-of-care software programs to administer self-report instruments and formulate a plan to implement MBC in their practice.

Literature References:

- Kessler, R.C., et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama, 2003. 289(23): p. 3095-105.
- Trivedi, M.H., et al., Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry, 2006. 163(1): p. 28-40.

3:45 p.m. - 5:45 p.m.

Special Session

HOW TO USE THE MODEL PSYCHOPHARMACOLOGY CURRICULUM IN VARIOUS TEACHINGS

Ira Glick, Stanford University School of Medicine

Overall Abstract: This workshop will focus on how to teach cutting edge clinical psychopharmacology for a) psychiatric residents, b) primary care physicians, c) medical students in the US and globally. The target audience is program directors, Chairs, and teachers of psychopharmacology and psychiatry.

Learning Objectives:

- At the conclusion of this presentation, the student will be aware of recent advances in psychopharmacology for medical students.
- At the conclusion of this presentation, the student will be aware of recent advances in psychopharmacology for primary care physicians.

MEDICAL MARIJUANA: PROMISE AND PERIL*

Susan Weiss, National Institute of Health/NIDA

Overall Abstract: To date, twenty-three states plus the District of Columbia (DC) have passed laws legalizing marijuana for medical purposes and fifteen additional states have legalized a component of marijuana, cannabidiol, for medicinal use. Four states plus DC have legalized its recreational use for individuals over age 21. Several additional states are likely to consider legal changes to the status of marijuana this year.

These changes have largely occurred without significant input from the scientific and medical research communities. Consequently, the degree to which the current evidence base was considered in the medical marijuana laws is highly variable. The FDA has approved the primary active ingredient in marijuana, THC, for two indications—cachexia (or wasting) associated with AIDS, and nausea induced by cancer chemotherapy. Other countries have approved nabixmols (Sativex) for the treatment of pain and spasms associated with multiple sclerosis. However, there remains significant disagreement, and varying levels of evidence, regarding the acceptability and effectiveness of marijuana and its constituents as a treatment for cancer, epilepsy, multiple sclerosis, PTSD, ADHD, Alzheimer's disease, insomnia, pain, and more.

of special interest to clinicians

This symposium will address a number of topics, including the promise of the endocannabinoid system for medication development, the risks associated with medical and recreational use of marijuana, the state of the current science regarding the use of marijuana for clinical disorders, and the status of medical marijuana laws and programs in the US and Canada.

Learning Objectives:

- Participants will learn the current state of knowledge regarding the endocannabinoid system and its underlying role in brain function related to treating brain disorders, and receive an update on the status of clinical research on pain and other key putative indications treated by marijuana.
- Participants will learn the risks associated with marijuana use, including acute effects on mood, cognitive behavior, and performance, as well as risks associated with chronic use, such as psychosis, addiction and others.
- Participants will learn about the current national system to provide marijuana to patients in Canada, including physician guidelines, indications, and patient registries.

MEDICAL MARIJUANA FOR PSYCHIATRIC INDICATIONS: IS THE CART BEFORE THE HORSE?

Deepak D'Souza, Yale University School of Medicine & VACHS

Individual Abstract: Background: In many states marijuana has been approved for a number of psychiatric conditions including post-traumatic stress disorder (PTSD), agitation in Alzheimer's disease (AD) and Tourette's syndrome (TS). The purpose of this presentation is to review the evidence supporting the use of marijuana for psychiatric indications. Methods: The literature was searched using terms related to marijuana and other cannabinoids and specific diagnoses. The best quality of evidence i.e., double-blind, randomized, placebo-controlled clinical trials (RCTs) and meta-analyses was sought, and in the absence of RCTs the next best available evidence (observational studies, case reports, etc.) was reviewed.

Results: There are no RCTs investigating the efficacy of marijuana for psychiatric indications. The available evidence comes from lower quality studies. The strength of evidence for the use of cannabinoids (marijuana, THC and nabilone) for psychiatric conditions is very low. In contrast, the chronic use of cannabinoids has been associated with a number of negative consequences.

Discussion: In light of limited evidence for the therapeutic use of marijuana for psychiatric indications, and the known risks of cannabinoids, the use of cannabinoids for psychiatric disorders is premature. There is an urgent need for research that has the potential to yield high quality evidence and to inform the debate on the clinical utility of cannabinoids for psychiatric disorders. Furthermore, if marijuana is approved for "medical" reasons under physician oversight, it needs to be subjected to the same standards of evidence that are applied to other drugs that are FDA approved.

Learning Objectives:

- The available evidence supporting the clinical utility of cannabinoids for psychiatric conditions.
- The risks associated with chronic exposure to cannabinoids.

Literature References:

- Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. Hill KP. JAMA. 2015 Jun 23-30;313(24):2474-83. doi: 10.1001/jama.2015.6199. Review. PMID: 26103031
- Medical Marijuana: Is the Cart Before the Horse? D'Souza DC, Ranganathan M. JAMA. 2015 Jun 23-30;313(24):2431-2. doi: 10.1001/jama.2015.6407

MEDICAL MARIJUANA IN 2016: WHAT A CLINICIAN NEEDS TO KNOW

Kevin Hill, McLean Hospital

Individual Abstract: As of March 2016, twenty-three states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws; thus we will review the pharmacology, indications, and laws related to medical marijuana use. The medical literature on medical marijuana with an emphasis on 28 RCTs of cannabinoids as pharmcotherapies for indications other than those approved by the US FDA-approved cannabinoids (dronabinol and nabilone). The evidence suggests that the best evidence for medical marijuana beyond the two current FDA indications is for chronic pain, neuropathic pain, and muscle spasticity due to multiple sclerosis. Medical marijuana is used to treat a host of indications, a few of which have evidence to support them and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and by patients who will benefit from its use.

Learning Objectives:

- Summarize the policies addressing the use of marijuana as a medication in United States.
- Identify the risks and benefits of marijuana when used medically, as well as alternatives to marijuana.

Literature References:

- Kleber HD, DuPont RL. Physicians and medical marijuana. Am J Psychiatry. 2012 Jun;169(6):564-8.
- Hill KP. Clinical Crossroads: Medical Marijuana for the Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Systematic Review. JAMA. 2015 Jun 23-30;313(24):2474-83.

THE ENDOCANNABINOID SYSTEM AS A TARGET FOR THERAPEUTIC DRUGS

Daniele Piomelli, University of California, Irvine

Individual Abstract: The major psychoactive constituent of cannabis, Δ9-tetrahydrocannabinol, affects pain, emotion and energy balance in humans and laboratory animals by activating CB1-type cannabinoid receptors in the brain and peripheral tissues. The two primary endogenous ligands of these receptors are the lipid-derived transmitters, anandamide and 2-arachidonoylglycerol (2-AG). Anandamide and 2-AG are released in select regions of the brain and are deactivated through a two-step process consisting of transport into cells followed by intracellular hydrolysis. Anandamide hydrolysis is catalyzed by fatty-acid amide hydrolase (FAAH), while 2-AG hydrolysis is primarily mediated by monoacylglycerol lipase (MGL). In my talk, I will describe the pharmacological properties of various new drug classes, which interfere with endocannabinoid signaling. These include

centrally active FAAH inhibitors such as URB597 and peripherally restricted FAAH inhibitors such as URB937.

Learning Objectives:

- Understand the basic properties of the endogenous cannabinoid system.
- Acquire a broad appreciation of how this system may intervene in pathology and might be exploited for therapy.

Literature References:

- Piomelli D. More surprises lying ahead. The endocannabinoids keep us guessing. Neuropharmacology. 2014 Jan;76 Pt B:228-34. doi: 10.1016/j.neuropharm.2013.07.026.
- Wei D, Lee D, Cox CD, Karsten CA, Peñagarikano O, Geschwind DH, Gall CM, Piomelli D. Endocannabinoid signaling mediates oxytocin-driven social reward. Proc Natl Acad Sci U S A. 2015 Nov 10;112(45):14084-9. doi: 10.1073/pnas.1509795112.

MEDICAL MARIJUANA IN CANADA

Didier Jutras-Aswad, Centre hospitalier de l'Université de Montréal

Individual Abstract: Description of the specific purpose: While the debate surrounding marijuana use, its adverse effects and its therapeutic potential continues to divide experts, the Canadian federal government has developed a national program to regulate its therapeutic use. The system surrounding medical marijuana in Canada is a relatively complex set of rules designed to regulate a commercial industry that produces and distributes marijuana for medical purposes. In addition to ensuring that patients can access quality-controlled marijuana produced under optimal conditions, these regulations also set out a number of steps that a patient must follow to obtain medical marijuana from a licensed producer. The objective of this presentation is to provide an overview of the system surrounding medical marijuana in Canada.

Content: This presentation will review how the medical marijuana system works in Canada, including the regulations for production and distribution and the process that allows patients to be approved and have access to medical marijuana. Regulations surrounding the prescribing of medical marijuana by physicians, indications and clinical guidelines as well the patient register that must be established will also be covered.

Methodology: This presentation will provide a critical review of the available literature and publications related to medical marijuana regulations in Canada.

Results: While the procedures for accessing marijuana for medical purposes identify the steps a patient must follow to have access to this treatment, a number of questions remain unanswered. Issues related to production, access, prescribing guidelines for physicians as well as the distribution of medical marijuana will have to be clarified. The complex interplay between medical marijuana and recreational use of this substance also contributes to the current debate surrounding this set of regulations.

Importance of the presentation: This presentation will provide an opportunity to discuss the Canadian experience with respect to the regulation of medical marijuana, to identify research and regulatory priorities, and to compare Canadian regulations with those in other jurisdictions.

Learning Objectives:

- Review the main features of the system surrounding medical marijuana in Canada.

of special interest to clinicians

- Discuss limitations and pending issues with respect to the regulation of medical marijuana in Canada.

Literature References:

- Marihuana for Medical Purposes Regulations (SOR/2013-119), Government of Canada, Ottawa, Canada.
- Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids. 2013. Abramovici, H. Controlled Substances and Tobacco Directorate, Health Canada, Ottawa, Canada.

Friday, June 3, 2016

8:30 a.m. - 10:00 a.m.

Friday Morning Panel Sessions*

SHARED PHARMACOLOGICAL TARGETS FOR SUBSTANCE USE AND OTHER PSYCHIATRIC DISORDERS

Ivan Montoya, DHHS/National Institute on Drug Abuse

Overall Abstract: Substance use disorders (SUDs) and other psychiatric disorders appear to share many neurobiological mechanisms and pathways. Compounds that have effects on these shared pathways may be effective to treat both types of disorders. The purpose of this symposium is to present three examples of compounds that are being developed to treat other psychiatric disorders that may also be efficacious for SUDs because these common neurobiological targets. The first compound is Volinanserin, a selective 5-HT2A receptor antagonist is being developed to treat psychosis associated with Parkinson's Disease, which may also be effective in the treatment of cocaine use disorders. The second compound is PF-04457845, a fatty acid amide hydrolase (FAAH) inhibitor that may be effective for treating pain and inflammation; this compound is also being evaluated for efficacy in cannabis use disorders. The third compound, ALKS-5461 is a combination of samidorphan (a selective μ antagonist) and buprenorphine (μ opioid receptor partial agonist, κ opioid receptor antagonist, and nociception receptor (ORL-1) partial agonist. This compound is under development as an adjunct in treatment-resistant depression and may also be useful in treating cocaine use disorders. These presentations will provide information about the safety and efficacy of these compounds as well as the mechanistic bases for the treatment of SUDs and other neuropsychiatric disorders. Although these shared pharmacological targets may be effective for comorbid conditions that are highly prevalent (e.g., depression and SUDs), the symposium will also bring up the notion that these shared targets may transcend psychiatric comorbidities.

Learning Objectives:

At the end of the symposium, the participants will:

- Learn about the safety and efficacy of volinanserin, PF-04457845, and ALKS-5461 for the treatment of SUDs and other neuropsychiatric disorders.
- Understand the relevance of evaluating compounds with effects on pharmacological targets shared by SUDs and other psychiatric disorders.

PIMAVANSERIN: A NEW TREATMENT FOR PARKINSON'S PSYCHOSIS THAT MAY HAVE EFFICACY AS A TREATMENT FOR COCAINE USE DISORDERS

Jane Acri, NIDA/NIH/DTMC

Individual Abstract: Pimavanserin is a selective 5HT2A inverse agonist. Serotonin receptors mediate a vast number of physiological phenomena in the brain and have been implicated in neuropsychiatric disorders. The 5HT2A receptor is one of 14 GPCRs distributed throughout the brain.

While most antipsychotic drugs achieve their primary effects through the blockade of dopamine D2 receptors, many also block the 5HT2A receptor which contributes to their efficacy. Because Parkinson's disease is characterized by dopaminergically-mediated movement disorders, patients with Parkinson's disease Psychosis (PDP) cannot tolerate most antipsychotic medications without exacerbation of primary symptoms. Acadia Pharmaceuticals has developed pimavanserin as a selective 5HT2A inverse agonist for the treatment of PDP (Cummings et al., 2014). In double-blind placebo-controlled trials, pimavanserin as demonstrated sufficient efficacy that it has been submitted for NDA and has been given the status of breakthrough therapy. It is expected to be clinically available soon.

Serotonin receptor subtypes have long been of interest for substance use disorders because of their role in the regulation of dopaminergic signaling in key brain areas including striatum, VTA, nucleus accumbens and prefrontal cortex. In particular, agonists of 2HT2C receptors and antagonists at 2HT2A receptors, which play complementary roles in the regulation of dopamine signaling, have been of interest, and a great deal of data has been generated (see review by Bubar and Cunningham, 2008). Up until recently, the only selective ligands for either receptor have been research tool compounds, so the translational relevance of the preclinical studies suggestive of efficacy as a cocaine treatment was limited. However, now that compounds interacting with these receptors are becoming clinically available, it is likely that the situation will change and these compounds can be advanced to clinical trials. In preclinical models, pimavanserin has been shown to reduce cocaine self-administration in rhesus monkeys, and to reduce cocaine cue-induced reinstatement in rats previously trained to self-administer cocaine. Ongoing studies are assessing its effect on cue reactivity in rodents and it is hoped that pimavanserin will soon be evaluated for effects on cue reactivity and cocaine craving in humans.

The clinical data on pimavanserin for PDP and preclinical data suggestive of efficacy for cocaine use disorders will be presented. The clinical availability of pimavanserin will advance the field of substance use disorder treatment.

Learning Objectives:

- The development of Pimavanserin as a treatment of Parkinson's disease psychosis will be presented.
- The rationale for blockade of the 5HT2A receptor as a potential treatment target for cocaine use disorders, preclinical data on pimavanserin on animal models of cocaine dependence (self-administration and reinstatement).

Literature References:

- Bubar, M.J., and Cunningham, K.A. (2008). Prospects for serotonin 5-HT2R pharmacotherapy in psychostimulant abuse. Prog. Brain Res. 172: 319-346.

of special interest to clinicians

- Cummings J., Isaacson S., Mills R., Williams H., Chi-Burris K., Corbett A., Dhall R., Ballard C. (2014) Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. Lancet 383: 533-40.

CHARACTERIZATION OF AGONIST-ANTAGONIST OPIOID MODULATION WITH ALKS 5461 IN MAJOR DEPRESSION

Elliot Ehrich, Alkermes, plc

Individual Abstract: Accumulating preclinical and clinical evidence indicate that major depressive disorder (MDD) is associated with significant dysregulation of the endogenous mu and kappa opioid systems. The contemporary use of exogenous opioids to treat MDD and related mood disorders, however, is limited due to their potential for abuse and addiction. In order to therapeutically address endogenous opioid dysregulation in MDD while avoiding abuse and addiction, we studied a combination of buprenorphine (BUP) and samidorphan (SAM), a potent μ opioid antagonist.

Fixed ratios of BUP and SAM were co-formulated in a single sublingual tablet (ALKS 5461). Pupilometry and subjective pharmacodynamic effects of ALKS 5461 were evaluated in non-addicted opioid experienced subjects. Maximal blockade of pupilary and opioid subjective effects was observed with a 1:1 ratio of BUP: SAM. In a pilot study and a follow-up phase 2 study in subjects with MDD and an inadequate response to SSRI or SNRI therapy, adjunctive treatment with ALKS 5461 with a 1:1 BUP: SAM ratio demonstrated evidence of clinically important antidepressant efficacy versus placebo. Large phase 3 studies are ongoing.

Microdialysis studies in rats showed that BUP/SAM administration modulated release of dopamine, serotonin, and/or metabolites in the nucleus accumbens (NAc) shell, medial prefrontal cortex (mPFC).

"Balanced" agonist-antagonist opioid modulation with ALKS 5461 is a promising treatment approach for patients with MDD and an inadequate response to standard antidepressant therapy. The combination may have further clinical utility in the treatment of other psychiatric and substance use disorders associated with endogenous opioid dysregulation.

Learning Objectives:

- Learn about the role of endogenous opioid dysregulation in the context of major depressive disorder.
- Understand the potential utility of combined opioid agonist-antagonist as treatment of MDD, and other psychiatric and substance use disorders.

Literature References:

- Lutz PE, Kieffer BL. Opioid receptors: distinct roles in mood disorders. Trends Neurosci 36[3], 195-206. 2013
- Ehrich E, Turncliff R, Du Y, Leigh-Pemberton R, Fernandez E, Jones R, Fava M. Evaluation of opioid modulation in major depressive disorder. Neuropsychopharmacology 40[6], 1448-1455. 2015.

TESTING THE EFFICACY AND SAFETY OF A FAAH-INHIBITOR IN THE TREATMENT OF CANNABIS DEPENDENCE

Deepak D'Souza, Yale University School of Medicine & VACHS

Individual Abstract: Background: Cannabis is the most widely used illicit drug worldwide. Cannabis dependence is associated with tolerance and withdrawal. There are no FDA approved treatments there are no clearly effective FDA approved treatments. Substitution treatment with dronabinol (THC) may reduce cannabis withdrawal syndrome (CWS) but its therapeutic potential is limited by its psychoactive effects, abuse liability, and by its limited relapse prevention effects. An alternative to substitution treatment may be to potentiate signaling through the endogenous cannabinoid system.
Anandamide a principal endocannabinoid is broken down by the enzyme fatty acid amide hydrolase (FAAH). Recently, a FAAH inhibitor which increases anandamide levels was shown to reduce CWS in THC-dependent animals. Compared to THC or cannabis, FAAH-inhibitors 1) may not have psychoactive effects, 2) are not rewarding, 3) do not increase the abuse liability of other addictive drugs, 4) are not associated with tolerance and 5) produce fewer changes in CB1-R function. PF-04457845 is an orally active, long-acting, potent and selective FAAH inhibitor that does not have psychoactive or cognitive effects and is well-tolerated at the proposed dose. It does not have effects suggestive of abuse liability or discontinuation-related withdrawal symptoms.

Hypothesis: The FAAH-Inhibitor PF-04457845 will attenuate cannabis withdrawal syndrome, reduce cravings and reduce relapse rates in cannabis dependent individuals. Cannabis-dependent subjects (n= 60) with a history of CWS were randomized to receive PF-04457845 (4mg) or placebo a 2:1 ratio in a double-blind, placebo-controlled, parallel group study. After a screening period, subjects entered a 4-week treatment phase. Subjects were hospitalized on an inpatient research unit for up to 1 week to achieve abstinence and precipitate CWS. Subjects continued the remaining 3 weeks of treatment as outpatients. The treatment phase was followed by an 8 week follow up phase to assess the durability of any treatment effects. Urine toxicology for THC-COOH, cannabis use, withdrawal symptoms, craving for cannabis, self-report of sleep and appetite, sleep architecture, mood, cognition, serum endocannabinoid levels were measured. Adherence to study medication was assessed almost daily by video confirmation using Cellphone Assisted Remote Observation of Medication Compliance (CAROMA).

The study has enrolled 55 of 60 subjects and projected to be completed shortly. The study medication has been well tolerated. There have been no serious adverse events. Adherence to study medication was very high. Results of this study will be available to be presented.

Learning Objectives:

- Learn about the endocannabinoid system comprising of 2 receptor, the endocannabinoids anandamide and 2-AG, the symethesis and degradation of these endocannabinoids, and the effects of activating cannabinoid receptors.
- Learn about changes to the endocannabinoid system following repeated exposure to cannabis.

Literature References:

- Chemical probes of endocannabinoid metabolism. Blankman JL, Cravatt BF. Pharmacol Rev. 2013 Mar 19;65(2):849-71. doi: 10.1124/pr.112.006387. Print 2013 Apr. Review. PMID:23512546
- Budney AJ, Hughes JR, Moore BA, Novy PL: Marijuana abstinence effects in marijuana smokers maintained in their home environment. Arch Gen Psychiatry 2001; 58(10):917-24

of special interest to clinicians

PSYCHOTHERAPY, PHARMACOTHERAPY AND DEVICES TO TREAT BIPOLAR II DEPRESSION: NEW EVIDENCE*

Holly Swartz, University of Pittsburgh School of Medicine

Overall Abstract: Although sometimes deemed a "milder" form of bipolar disorder because of lower rates of psychosis and hospitalization, bipolar II disorder (BD II) is associated with significant morbidity and high rates of mortality. Characterized by multiple, protracted depressive episodes, BD II is at least as disabling—some would suggest more disabling—than bipolar I disorder (BD I). Although the phenotypes differ on many parameters, approaches to management of BD II have paralleled strategies for treating BD I. Not surprising, treatments used for BD I may behave differently in those with BD II. For instance, antidepressant medications may be more effective in BD II relative to BD I and less likely to cause switching. Similarly, psychotherapy as a stand-alone treatment is contraindicated in BD I but may be indicated for some individuals with BD II. Despite pressing clinical need, the empirical evidence for BD II treatments is very limited.
This symposium will explore recent advances in treatments for BD II depression including evidence from a randomized trial of pharmacotherapy for BD II (Suppes), results from a new study evaluating the role of Interpersonal and Social Rhythm Therapy in the management of BD II depression (Swartz), and promising data from a trial of cranial electrotherapy stimulation (Galynker). Presenters will discuss evidence-based approaches to management of BD II as well as the need for continued research to understand optimal strategies to treat this common and disabling BD phenotype.

Learning Objectives:
At the end of this session, participants will be able to:

- Identify evidence supporting treatment strategies for bipolar II disorder.
- Improve their understanding of bipolar II disorder.

A RECENT TREATMENT STUDY ADDRESSING IF BIPOLAR II RESPONSE TO TREATMENT REALLY IS THE SAME AS BIPOLAR I DISORDER

Trisha Suppes, Stanford University

Individual Abstract: Few treatment guidelines directed towards medication management of bipolar disorder address differences between patients with bipolar I versus bipolar II disorder (BDI; BDII). Often there is no mention of BDII or if there is the recommendations are to just use what has been studied for patients with BDI. There are few randomized double-blinded controlled trials enrolling reasonable numbers of BDI and BDII patients. The studies of quetiapine are one of our clearest examples where both types of bipolar disorder were enrolled in double blind controlled trials. These studies raise interesting questions not only of possible differences in treatment response but also the question of tolerability differences – often not considered adequately in considerations of response to medications.
A recent completed controlled study in patients with BDII addressing the response and tolerability to antidepressants will be presented (Altshuler, Sugar, McElroy et al). In this double-blind randomized trial comparison of mono therapy sertraline, lithium, or the combination, tolerability including switch rates was a primary outcome followed by treatment response. In this 16-week study of patients with BDII currently depressed (n=146), little difference in switch rate or response rate was observed between the 3 double blinded study

groups, though dropout rate was higher in the combination group. Further details of results will be presented.

Based on results from this controlled study, the potential role for antidepressants in treatment of BDII will be discussed in light of published studies examining treatment response and tolerability. This topic is of particular importance given the apparently different result from many studies on antidepressant response for patients with BDI in comparison to BDII.

Learning Objectives:

- To discuss whether the use of antidepressants in patients with bipolar II disorder causes switch based on the study results reported in this panel.
- To be able to discuss the response to antidepressants in bipolar II versus bipolar I disorder.

Literature References:

- Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PK, Landen M. The Risk of Switch to Mania in Patients With Bipolar Disorder During Treatment With an Antidepressant Alone and in Combination With a Mood Stabilizer. Am J Psychiatry 2014
- Swartz HA, Thase ME. Pharmacotherapy for the treatment of acute bipolar II depression: current evidence. J Clin Psychiatry 2011;72:356-366
- Altshuler LL, Suppes T, Black DO, Nolen WA, Leverich G, Keck PE, Jr., Frye MA, Kupka R, McElroy SL, Grunze H, Kitchen CM, Post R. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. Am J Psychiatry 2006;163:313-315

INTERPERSONAL AND SOCIAL RHYTHM THERAPY AND QUETIAPINE AS TREATMENTS FOR BIPOLAR II DEPRESSION

Holly Swartz, University of Pittsburgh School of Medicine

Individual Abstract: Psychotherapy has not been systematically evaluated in Bipolar II Disorder (BD II), even though psychotherapy may play an important role in the management of BD II. Many individuals struggle with issues that lend themselves to psychosocial remediation such the challenge of differentiating hypomania from well periods and the negative impact of illness on relationships. This study compared Interpersonal and Social Rhythm Therapy (IPSRT) plus placebo to IPSRT plus quetiapine as treatments for BD II depression. Unmedicated adults (n=92) with BD II and a major depressive episode were randomly assigned to interventions and followed for 20 weeks.

Both treatments yielded comparable response rates, defined as ≥50% reduction in Hamilton Rating Scale for Depression (HRSD-25) scores from baseline: 67.4% (62/92) in the entire sample, with no between-group differences. Both groups improved significantly over time but there was a significant time X group interaction favoring IPSRT + quetiapine on the HRSD-17 ($F=3.924$, $df=1115.4$, $p=.048$) and YMRS ($F=4.242$, $df= 58.5$, $p=.044$). Those assigned to IPSRT + quetiapine developed significantly higher BMI over time ($F=6.671$, $df=67.96$; $p=.012$).

Participants improved with both IPSRT alone and IPSRT plus quetiapine. Quetiapine, an efficacious treatment for BD II, is also associated with increased risk for metabolic burden. Not surprisingly, IPSRT plus quetiapine resulted in greater symptomatic improvement but

also more weight gain than IPSRT alone. IPSRT monotherapy may be appropriate treatment for BD II.

Learning Objectives:

- Identify evidence-based psychotherapy as a treatment modality that may play a role in the management of bipolar II disorder.
- Understand the risks and benefits associated with combining pharmacotherapy and psychotherapy to treat bipolar II depression.

Literature References:

- Swartz HA, Frank E, Cheng Y. A randomized pilot study of psychotherapy and quetiapine for the acute treatment of bipolar II depression. Bipolar Disords. 2012;14:211-216.
- Swartz HA, Levenson JC, Frank E. Psychotherapy for bipolar II disorder: The role of interpersonal and social rhythm therapy. Prof Psychol Res Pr. 2012;43 145-153.

SAFETY AND EFFICACY OF CRANIAL ELECTROTHERAPY STIMULATION IN TREATMENT OF BIPOLAR II DEPRESSION

Igor Galynker, Icahn School of Medicine at Mount Sinai

Individual Abstract: Bipolar depression is difficult to treat, as evidenced by the marginal efficacy offered by existing treatments. Cranial Electrotherapy Stimulation (CES) has been shown to be effective in the treatment of unipolar depression; however, its effectiveness in the treatment of bipolar II depression has not yet been examined in a clinical trial. In this context, we have evaluated the efficacy of CES for the treatment of bipolar II depression. In this double-blind study, sixteen participants were randomly assigned to either a sham or active group. For 2 weeks, 2 mA of CES treatment was administered to the active group, with the sham group receiving a sham treatment. Symptom non-remitters from both groups received an additional 2 weeks of open-label active treatment. Outcome was measured using the Beck Depression Inventory (BDI).

CES was associated with a significant decrease in BDI scores from baseline to the second week (p=.003) maintaining significance until week 4, (p=.002). The sham group showed a significant decrease on BDI scale scores from baseline to week one (p=.034) but no significant change from baseline to end of week 2. The mean change from baseline to week 2 was significantly different between groups for BDI (p=.016), with the active treatment group showing greater improvement. There was no difference between the groups in side effect frequency.

The results of this small study indicate that CES may be a safe and effective treatment for BD II suggesting that further studies on safety and efficacy of CES may be warranted.

Learning Objectives:

Participants will be able to:

- Appreciate the mechanism of action and distinct characteristics of Cranial Electrical Stimulator among other non-invasive medical treatments.
- Appreciate the encouraging initial findings on efficacy of Cranial Electrical Stimulation in treatment of bipolar II depression.

Literature References:

- Bystritsky A, Kerwin L, Feusner J. A pilot study of cranial electrotherapy stimulation for generalized anxiety disorder. J Clin Psychiatry 2008;69:412-417.
- Barclay T, Barclay R. A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. J Affect Disord 2014;164:171-177.
- Feusner J, Madsen S, Moody T et al. Effects of cranial electrotherapy stimulation on resting state brain activity. Brain And Behavior 2012;2:211-220.

APPLICABILITY OF INDUSTRY/REGULATORY ANTIDEPRESSANT CLINICAL TRIALS TO CLINICAL PRACTICE

Arifulla Khan, Northwest Clinical Research Center

Overall Abstract: Over the past thirty years regulatory agencies have approved more than fifteen antidepressants. Over 50,000 depressed patients have participated in pharmaceutical company sponsored research. Both published versions of the clinical trials database and unpublished regulatory summaries of the approval programs have played a significant role in the clinical management of depressed patients.
However, recent scrutiny of the way these data have been used in clinical management have raised questions about how best to apply these data in clinical practice. This panel is designed to consider if the validity and the utility of these industry sponsored data lend themselves to application in the routine management of depressed patients.

Learning Objectives:

- Appreciate the level of differences between antidepressant clinical trial participants and clinical practice depressed patients.
- Appreciate the limitations of antidepressant clinical trial data as applied to clinical practice.

DO DEPRESSED PATIENTS IN REGISTRATION CLINICAL TRIALS REFLECT THE "REAL WORLD" PRACTICE?

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: Over the past few decades, we have seen a progressive increase in placebo response rates in clinical trials of antidepressant therapies, and such phenomenon has been puzzling to clinicians who struggle to obtain placebo effects in their practice. Phase II and III clinical trials for depression typically enroll participants with major depressive disorder (MDD) according to stringent inclusion and exclusion criteria. The presence of a placebo control arm, as well as the uncertainty about the efficacy of a novel compound, may also reduce the patients' motivation and willingness to participate in a clinical trial for MDD and may lead to the enrollment of less severely ill patients. Furthermore, investigators may be biased to recruit subjects for their trial even when they do not quite meet the exact inclusion criteria or do not reflect the disease, but rather the response to adverse and stressful circumstances. All these factors may contribute to the fact that these patients may not be representative of typical depressed patients seeking treatment in a "real world" practice. We have analyzed data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, which used broad inclusion and minimal exclusion criteria and was more of an effectiveness trial, to evaluate whether typical phase II and III clinical trials recruit representative depressed outpatients. Of 2,855 STAR*D study participants, 22.2% met typical entry criteria for phase II and III clinical trials (efficacy sample) and 77.8% did not

(non-efficacy sample). The efficacy sample had a shorter average duration of illness and lower rates of family history of substance abuse, prior suicide attempts, and anxious and atypical symptom features. This analysis suggested that Phase II and III trials do not typically recruit representative treatment-seeking depressed patients. Our group at MGH has independently interviewed (SAFER interviews) over 6,000 patients deemed appropriate for enrollment in phase II and phase III clinical trials of MDD and we have found a significant proportion of patients lacking both face validity (e.g., the patient's presentation is consistent with our knowledge of MDD) and ecological validity (e.g., the patient's symptoms reflect the characteristics of the illness in a real-world setting). As a field, we need to consider approaches to study design that increase the degree of representativeness of the "real world" among patients enrolled in registration trials of MDD, while enhancing the diagnostic precision of our efforts, thereby improving both face and ecological validity of patient participants.

Learning Objectives:

- Participants will become familiar with the differences observed between patients typically enrolled in registration trials for MDD and "real world" MDD patients.
- Participants will also learn about the strategies that can increase the representativeness of "real world" patients in registration trials of MDD, as well as their diagnostic precision.

Literature References:

- Wisniewski SR, Rush AJ, Nierenberg AA, Gaynes BN, Warden D, Luther JF, McGrath PJ, Lavori PW, Thase ME, Fava M, Trivedi MH. Can phase III trial results of antidepressant medications be generalized to clinical practice? A STAR*D report. Am J Psychiatry. 2009 May;166(5):599-607.
- Targum SD, Pollack MH, Fava M. Redefining affective disorders: relevance for drug development. CNS Neurosci Ther. 2008 Spring;14(1):2-9.

SHOULD THE LACK OF GENERALIZABILITY OF ANTIDEPRESSANT EFFICACY TRIALS HAVE IMPLICATIONS FOR PRODUCT LABELLING?

Mark Zimmerman, Brown University

Individual Abstract: Challenges to the generalizability of antidepressant efficacy trials (AETs) to patients treated in the real world have been raised for decades. More than a decade ago our clinical research group found that the vast majority of depressed patients presenting for treatment to our outpatient practice would have likely been excluded from in an AET because they did not meet the study's inclusion and exclusion criteria. Subsequent studies replicated our finding that most depressed outpatients treated in clinical practice would not qualify for an AET. Moreover, there was some evidence that treatment response differed between outpatients who would and would qualify for an AET.

Recently, we conducted a comprehensive review of placebo-controlled AETs published over the past 20 years in order to determine whether there have been any changes in these criteria subsequent to the publications that highlighted the unrepresentativeness of the depressed patients studied in AETs. We identified 170 placebo-controlled AETs published during the past 20 years, 56 of which were published during the past 5 years. The more recent studies were significantly more likely to exclude patients with comorbid Axis I disorders and personality disorders, exclude patients because the episode duration is too long or too short,

and exclude patients who made a suicide attempt in the past. The severity threshold on depression rating scales required for inclusion was higher in the more recent studies.

The results of the review suggested that in inclusion/exclusion criteria for AETs have narrowed over the past five years thereby suggesting that AETs are even less generalizable than they were previously (when concerns about their generalizability had already been raised).

According to the FDA's regulations the criteria used to select patients into registration studies should be addressed in a product's label. The FDA's labeling guidelines, which specifically indicate that the routine exclusion of patients of a certain level of severity should be noted in the label, has been uniformly ignored.

Learning Objectives:

- At the conclusion of this presentation the participant should become familiar with the changes in the inclusion/exclusion criteria used in placebo-controlled studies of antidepressant medication over the past 20 years.
- At the conclusion of this presentation the participant should become familiar FDA guidelines regarding product labeling and how this is related to the exclusion criteria used in antidepressant efficacy trials.

Literature References:

- Zimmerman, M., Mattia, J.I. & Posternak, M.A. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice. American Journal of Psychiatry, 2002, 159, 469-473.
- Zimmerman, M., Clark, H.L., Multach, M.D., Walsh, E., Rosenstein, L.K., & Gazarian, D. Have Treatment Studies of Depression Become Even Less Generalizable?: A Review of the Inclusion and Exclusion Criteria in Placebo Controlled Antidepressant Efficacy Trials Published During the Past 20 Years. Mayo Clinic Proceedings, 2015, 90, 1180-1186.

INCIDENCE OF SUICIDAL BEHAVIOR AMONG ANTIDEPRESSANT CLINICAL TRIAL PARTICIPANTS: 1991-2013

Arifulla Khan, Northwest Clinical Research Center

Individual Abstract: The idea that antidepressants may worsen suicide risk is based on post-hoc analysis of data from placebo controlled antidepressant clinical trials conducted more than 15 years ago. In order to verify and replicate this finding, we reviewed and analyzed data on the frequency of suicidal behavior from FDA Integrated Safety Summary (ISS) reports of 14 new drug applications for antidepressants approved between 1991 and 2013 that included 47,009 patients.

Overall, using regression analysis indicated that assignment to antidepressant or placebo was not associated with either suicide rate ($p=0.85$) or suicide attempt rate ($p=0.23$). However, suicidal behavior rate decreased 90% in the 7 programs approved after 2000 compared to the 7 programs approved prior to 2000. Of the 52 suicides, 48 occurred in the earlier group of programs (Chi Square=29.6, $p<0.0001$) and of 263 suicide attempts, 231 occurred in the earlier group of programs (Chi Square=126.3, $p<0.0001$). Suicide rate was 639/100,000PEY in the earlier programs compared to 64/100,000PEY in the latter programs (Chi Square=472, $p<0.0001$). Rate of suicide attempt was 3,075/100,000PEY in the earlier programs and was 445/100,000PEY in the latter programs (Chi Square=2000, $p<0.0001$).

of special interest to clinicians

The results of our study suggest that suicidal behavior in adult antidepressant efficacy clinical trials is susceptible to large fluctuations due to factors not accessible to researchers. Thus, data from antidepressant clinical trials sponsored by the pharmaceutical companies may not accurately inform the practicing clinician about suicide risk with antidepressants.

Learning Objectives:

- Understand the methods used to assess suicide behavior risk in antidepressant clinical trials conducted by pharmaceutical companies and collated by the US FDA.
- Ability to apply suicide risk assessment in clinical practice based on population risk data as well as pharmaceutical industry sponsored clinical trial data.

Literature References:

- Khan A, Warner HA, Brown WA (2000) Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials. Arch Gen Psychiatry 57:311-17.
- Gibbons RD, Hur K, Bhaumik DK, Mann JJ (2005) The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry 2005;165-72.

THE INTERSECTION OF PHARMACOLOGY AND NEUROMODULATION IN TREATMENT REFRACTORY MOOD DISORDERS*

Michael Henry, Massachusetts General Hospital

Overall Abstract: Purpose: Neuromodulation based therapies (i.e. ECT, TMS, DBS) and ketamine have shown significant efficacy in otherwise treatment refractory mood disorders. This panel is designed to begin the discussion about what these different approaches have in common mechanistically.

Content: Dr. Cusin will present the data on ketamine and other pharmacologic approaches to treatment resistant mood disorders with an emphasis on potential mechanisms of action.

Dr. Henry will present the data on current ECT practice and imaging data to support a circuit based hypothesis for mechanism of action. Dr. Camporodon will present the data on TMS and DBS, with an explanation of the pacemaker model for mechanism of action.

Importance: Treatment resistant mood disorders are common yet potentially lethal illnesses with significant morbidity and financial cost to society. Emerging treatments dichotomize into Neuromodulatory or pharmacologic. This panel will facilitate the discussion about what they have in common and may offer insight into ways to optimize these treatments in clinical practice.

Learning Objectives:

- Participants will be able to describe the available data on the relative efficacy of ketamine, ECT, TMS, and DBS in treatment refractory mood disorders.
- Participants will be able to describe potential mechanisms of action for ketamine, ECT, TMS, and DBS in treatment refractory mood disorders.

CIRCUIT-LEVEL MECHANISM OF ACTION OF NEUROMODULATION THERAPIES

Joan Camprodon, Harvard Medical School/Massachusetts General Hospital

Individual Abstract: Therapeutic options for patients with affective, behavioral, or cognitive disorders include psychotherapy, pharmacotherapy, and neuromodulation. Neuromodulation therapies are also commonly known under the labels of brain stimulation or somatic therapies. They are a group of device-based techniques that target specific structures of the nervous systems via electrical modulation with the goal of therapeutically modifying pathological patterns of brain activity and circuit connectivity. These therapies grow from a systems neuroscience paradigm that emphasizes the role of neural circuits and their processing strategies in healthy brain function, pathophysiology, and therapeutics. In this talk, we will discuss the known mechanisms of action of these techniques with a focus on Transcranial Magnetic Stimulation (TMS) and Electroconvulsive Therapy (ECT).

Learning Objectives:

- To understand the mechanisms of action of Transcranial Magnetic Stimulation (TMS) at the circuit level.
- To understand the mechanisms of action of Electroconvulsive Therapy (ECT) at the circuit level.

Literature References:

- Camprodon, JA, Rauch, SL, Greenberg, BD, Dougherty, DD (eds.). Psychiatric Neurotherapeutics: Contemporary Surgical & Device-Based Treatments in Psychiatry. New York, NY: Humana Press (Springer), 2015.
- Camprodon JA, Kaur N, Rauch SL, Dougherty DD. Neurotherapeutics. In: Stern TA, Rosenbaum JF, Fava M, Biederman J, Rauch SL (eds.) The Massachusetts General Hospital Comprehensive Clinical Psychiatry, 2nd Edition (Ch. 46, pp. 518-524). Philadelphia, PA: Elsevier, 2015.

THE EFFECTS OF ECT ON THE DEPRESSED BRAIN: A META ANALYSIS OF IMAGING AND EEG STUDIES

Michael Henry, Massachusetts General Hospital

Individual Abstract: Recent developments in neurostimulation techniques and the use of ketamine have increased the number of treatments available for treatment resistant mood disorder. Despite these advances ECT remains the "gold standard" for treatment resistant depression. This presentation will summarize using a meta analysis approach, the available data on the CNS effects of ECT from the perspective of electroencephalogram (EEG), magnetic resonance, and emission tomographic imaging. In order to permit comparison between treatments, the clinical characteristics of the populations included in these studies will also be examined. The EEG and imaging data will be discussed with respect to the anticonvulsant and circuit hypotheses of ECT's mechanism of action.

Learning Objectives:

- Participants will be able to describe the clinical characteristics of the populations treated with ECT that have been studied with EEG and/or functional imaging techniques.
- Participants will be able to describe brain regions where functional changes occur and the nature of the changes that occur in the brains of individuals undergoing ECT.

Literature References:

- Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. Haq AU1,2, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ. J Clin Psychiatry. 2015 Oct;76(10):1374-84.

of special interest to clinicians

- A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. Bautovich A, Wang MJ, Martin D, Harvey SB, Loo C. Clin Psychiatry. 2015 Jul 21. [Epub ahead of print].

THE USE OF KETAMINE IN TREATMENT-RESISTANT DEPRESSION: FROM RESEARCH TO CLINICAL

Cristina Cusin, Massachusetts General Hospital

Individual Abstract: Numerous studies have reported the efficacy of single or multiple infusions of ketamine in Treatment-Resistant Depression, however the clinical trials have limitations, in particular regarding the selection of participants.
We present the organization and structure of an intranasal ketamine clinic for the treatment of patients with severe TRD and outcome data of the population currently served by the clinic.

Our experience and limitations encountered has a profound impact for the development of clinical treatment utilizing ketamine in psychiatric clinical settings, that are different from research settings.

Learning Objectives:

- State of art in ketamine research in TRD.
- Indication and contraindications for use of ketamine in clinical setting.

Literature References:

- Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, Hawton K, Cipriani A. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev. 2015 Sep 23;9:CD011612
- Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, Murrough JW. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014 Dec 15;76(12):970-6