Monday, June 16, 2014

PANEL
9:00 AM – 10:30 AM

PANEL OVERVIEW:
BIOLOGICAL APPROACHES TO TREAT SUBSTANCES USE DISORDERS
Phil Skolnick[1], Heather L. Davis[2], Stephen Brimijoin[3], Gary R. Matyas[4], Raye Z. Litten[5]
[1]NIDA/NIH, [2]Pfizer Vaccine Immunotherapeutics, [3]Mayo Clinic, [4]Walter Reed Army Institute of Research, [5]NIAAA
The pharmacological treatment of SUDs has traditionally focused on small molecule approaches (e.g., naltrexone, varenicline) that target specific proteins (e.g., a receptor) in the brain. An alternative to this pharmacodynamic approach is a pharmacokinetic strategy employing biologics. Biologics are macromolecules that do not cross the blood-brain barrier, but reduce the access of an abused drug to the brain either by sequestration or rapid enzymatic degradation. Biologics include immunotherapies (vaccines and monoclonal antibodies) and genetically modified enzymes that catalyze the degradation of an abused drug (e.g. cocaine) orders of magnitude more rapidly than the wild-type enzyme. The purpose of this symposium is to provide an overview of biologics in development. The panel will review the principles underlying these approaches, the challenges associated with developing biologics to treat substance use disorders, and the potential advantages of these approaches compared to traditional pharmacotherapies. Heather Davis (Pfizer) will discuss the development of a new anti-nicotine vaccine, NIC7, currently in Phase I clinical testing. Antibodies induced by this vaccine appear to have higher avidity for nicotine than earlier vaccines which failed to demonstrate adequate efficacy in clinical trials. Gary Matyas (WRAIR) will discuss the development of an anti-heroin vaccine. The rapid degradation of heroin is a formidable challenge to developing vaccines that will bind heroin and its active metabolite, and novel solutions to this challenge will be presented. Stephen Brimijoin (Mayo Clinic) will discuss studies that formed the basis for development of a mutated isoform of butyrylcholinesterase as a potential treatment for cocaine use disorders. Such isoforms are capable of hydrolyzing cocaine at rates thousands of times faster than the wild type enzyme and when delivered to subjects in stable form can reduce or eliminate cocaine reward. Moreover, these therapeutic effects can be dramatically extended by gene transfer of enzyme cDNA with viral vectors. In rodents, such gene transfer has resulted in long term (at least 6 month) resistance to cocaine relapse. Preclinical studies are currently ongoing in non-human primates. If gene transfer of such cocaine hydrolases proves effective and safe in such models, there may be potential for a long-lived therapy for cocaine use disorders.

Learning Objectives:
- The audience will learn about the principles underlying biological approaches to treating substance use disorders, the challenges associated with developing vaccines for small molecules, and the advantages (and disadvantages) of biological approaches compared to traditional pharmacotherapies.
- The audience will learn about the development of specific biological products to treat substance use disorders, including a nicotine vaccine currently in clinical development, a POC study using an engineered butrylcholinesterase capable of metabolizing cocaine.

- 1,000-fold more effectively than the wild type enzyme, a heroin vaccine, and gene transfer techniques which represent the next approach to treating substance use disorders.

INDIVIDUAL ABSTRACT:
GENETICALLY ENGINEERED BUTYRYLCHOLINESTERASE (TV-1380): AN INNOVATIVE APPROACH TO TREAT COCAINE DEPENDENCE
Phil Skolnick
NIDA/NIH
Cocaine abuse and dependence are problems with devastating medical and social consequences, and currently there is no reliable means to treat cocaine addiction and rescue from cocaine overdose. Human plasma butyrylcholinesterase (BChE) is known to contribute to cocaine hydrolysis and has been considered for use in treating cocaine addiction. Efforts to improve the catalytic efficiency of this enzyme have led to a quadruple mutant fused to recombinant human serum albumin, Albu-BChE, which consistently demonstrated its potential therapeutic benefit in a series of pharmacology experiments. Albu-BChE shows ability to hydrolyze cocaine with 1000- fold increase in catalytic efficiency as compared to wild-type BChE. The mutant fused BChE prevented signs of cocaine toxicity as well as selectively abolished cocaine-induced "reinstatement" of drug-seeking behavior when administered to rats and monkeys before cocaine challenge. These data support continuation of clinical development of Albu-BChE to evaluate its potential in treating cocaine addiction in human.

Learning Objectives:
- TV-1380 enhances cocaine metabolism, in a dose-dependent manner.
- Effects were most pronounced at the first cocaine infusion session (24 hours post-dose) but were sustained even 7 days post-TV-1380 dosing.
- Examination of the metabolite profiles suggests a TV-1380-induced shift in the metabolic path.

INDIVIDUAL ABSTRACT:
USE OF FUNCTIONAL ASSAYS TO DEVELOP A NOVEL ANTI-NICOTINE VACCINE
Heather L. Davis
Pfizer Vaccine Immunotherapeutics
Anti-nicotine vaccines induce antibodies (Ab) that reduce nicotine to brain. Ph2 testing of NicVax (Nabi) and CYT002-NicQb (NicQb; Cytos) showed the top 1/3 of Ab responders had better 1yr quit rates than placebo. Since Ab function depends on both quantity (titer) and quality (avidity), the poor overall efficacy of these early vaccines, despite induction of high Ab titers, may be due to low avidity Ab. NIC7 is a novel anti-nicotine vaccine that comprises a nicotine-like hapten conjugated to CRM197 and adjuvanted with aluminum hydroxide and a CpG TLR 9 agonist. It was developed using two different functional readouts, namely (1) reduction of nicotine distribution to the brains of immunized animals, and (2) nicotine-binding capacity of anti-nicotine Ab from vaccinated animals in an equilibrium dialysis assay. During development, it was discovered that several different molecular attributes of the antigen affected the functional responses in mice and this was mostly through influence on Ab avidity rather than Ab titer. Antibody function was also influenced by choice of adjuvant; addition of CpG enhanced both Ab titer and Ab avidity.NIC7 was compared to a NicQb mimetic in NHP. Reduction of nicotine to the brain compared to non-immunized controls was significantly greater with NIC7 (81%) than the NicQb mimetic (7%; $P<0.0001$). Even the NIC7 vaccine without CpG had better function

(33% reduction of nicotine to brain) despite having about 10-fold less Ab than the NicQb mimetic ($P<0.01$). Ab avidity was significantly higher with NIC7, especially with CpG) than the NicQb mimetic and this is thought to account for the greater functional Ab response in NHP.

Learning Objectives:

- To understand how both the amount and quality of the anti-nicotine antibody response contribute to antibody function (i.e. nicotine binding capacity).
- To appreciate how changes in antigen design and adjuvant choice can influence the functional antibody response with an anti-nicotine vaccine.

Literature References:

- McCluskie R.J., Pryde D.C., Gervais D.P., Stead D.R., Zhang N., Bemoit M., Robertson K., Kim I.-J., Tharmanathan T., Merson J.R. and Davis H.L.. (2013). Enhancing immunogenicity of a 3'aminomethylnicotine-DT-conjugate anti-nicotine vaccine with CpG adjuvant in mice and non-human primates. Int Immunopharmacol 16:50-56.
- Pryde D.C, Jones L.H., Gervais D.P., Stead D.R., Blakemore D.C., Selby M.D, Beal D.M., White P, Zhang N, Benoit M, Robertson K, Merson J.R., Davis H.L., and McCluskie M.J. (2013). Selection of a novel anti-nicotine vaccine: influence of antigen design on antibody function in mice. PLOS ONE 8: e76557

INDIVIDUAL ABSTRACT:
DEVELOPMENT OF A HEROIN VACCINE

Gary R. Matyas
Walter Reed Army Institute of Research

One novel approach to the treatment of drug abuse is to develop vaccines that prevent the pharmacological effects of the drug. Although the vaccines do not reduce the physical dependence of the drug in addicts, vaccines will prevent the drug-induced euphoria. They may also be practically important in preventing relapse and drug overdose by blocking or muting the pharmacological effects of the drug. The mechanism of protection of vaccines is to induce antibodies that bind to the drug, sequester it in the blood and prevent it from the crossing the blood-brain barrier. However, the development of vaccines to drugs of abuse presents a number of problems. The drugs are too small to be immunogenic when injected and therefore, surrogate drug haptens must be coupled to a carrier to induce antibody responses to the drug. Both high titer antibodies and high affinity antibodies that have a long duration are required. The vaccine will need a potent adjuvant to induce the high titer and long duration antibodies. Vaccine development against heroin is particularly difficult because heroin is rapidly metabolized to 6-acetylmorphine and morphine after injection. Consequently, a vaccine for heroin must induce antibodies that bind not only to heroin, but also its metabolites. Two heroin haptens, DiAmHap and MorHap, were tested as antigens for a candidate heroin vaccine. MorHap is a morphine analog containing the functional group used for coupling at the 6 hydroxyl position. DiAmHap is a heroin analog in which amide groups are substituted for the acetyl groups at the 3 and 6 hydroxyl positions. The functional coupling group in DiAmHap is at the bridge nitrogen at position 17. MorHap and DiAmHap were coupled to tetanus toxoid as the carrier and mixed with liposomes containing monophosphoryl lipid A (MPLA). Liposomes containing MPLA are safe and potent adjuvant and have been shown to induce high titer antibody responses in humans. Mice were immunized and boosted twice at 3 week intervals. Nine weeks after the primary immunization, sera were assayed for antibodies to the hapten and the animals were tested in a

hot-plate nociception assay. Antibody titers were very high with endpoint titers of 3 and 2.5 million for MorHap and DiAmHap immunized mice, respectively. Both groups of immunized animals exhibited reduced antinociceptive effects of heroin after the injection of heroin. Immunization with MorHap only induced antibodies that reacted with 6-acetylmorphine and morphine, whereas immunization with DiAmHap induced antibodies that reacted with heroin, 6-acetylmorphine and morphine. In contrast to the studies that demonstrated that only a metabolically degradable hapten can serve as a heroin vaccine (Schlosburg et al.), this study indicates that stable heroin haptens can be used in vaccine formulations and that resulting antibodies block the pharmacological effects of heroin. This work was supported by an Avant Garde award from the National Institute on Drug Abuse (NIH grant no. 1DP1DA034787-01) and through a Cooperative Agreement Award (no.W81XWH-07-2-067) between the Henry M. Jackson Foundation for the Advancement of Military Medicine and the U.S. Army Medical Research and Materiel Command.

Learning Objectives:

- Development of a heroin vaccine has significant challenges, including rapid metabolic degradation of heroin to pharmacologically active components. However, stable heroin analogs are able to induce antibodies that protect animals from the pharmacological effects of heroin.
- Vaccines to drugs of abuse are a viable future treatment option for substance abuse.

Literature References:

- Matyas GR, Mayorov AV, Rice KC, Jacobson AE, Cheng K, Iyer MR, Li F, Beck Z, Janda KD, Alving CR. Liposomes containing monophosphoryl lipid A: a potent adjuvant system for inducing antibodies to heroin hapten analogs. Vaccine. 2013 Jun 10;31(26):2804-10.
- Schlosburg JE, Vendruscolo LF, Bremer PT, Lockner JW, Wade CL, Nunes AA, Stowe GN, Edwards S, Janda KD, Koob GF. Dynamic vaccine blocks relapse to compulsive intake of heroin. Proc Natl Acad Sci U S A. 2013 May 28;110(22):9036-41.

INDIVIDUAL ABSTRACT:
CONTINUING TOWARDS GENE TRANSFER OF MODIFIED HUMAN BUTYRYLCHOLINESTERASE TO TREAT COCAINE ADDICTION

Stephen Brimijoin
Mayo Clinic

We are engaged in preclinical studies of a therapy for cocaine abuse based on viral gene transfer of an efficient cocaine hydrolase (CocH) derived by five active-site mutations in human butyrylcholinesterase (BChE). The goal is to demonstrate that a single treatment can deliver enzyme at levels that destroy cocaine before it reaches the brain and will sustain these levels indefinitely without adverse effects. Data from rat and mouse models prove that this goal is achievable with helper-dependent adenovirus and adeno-associated virus vectors that drive transgene expression in liver for at least two years after one i.v. injection. Using high-dose vector (10^13 viral particles/kg or greater), the levels of expressed protein rise 1000-fold or more above those of native BChE. Even though CocH does hydrolyze acetylcholine, this high-level expression has no detectable effects on cholinergic neurotransmission. In particular, neuromuscular function (grip strength, treadmill performance, and spontaneous locomotion) remains unchanged. We have also seen no deficits in maze learning and retention, or abnormalities in heart rate and other physiological functions tested to date. In contrast, CocH vector treatment has a large impact on behavioral responses to cocaine. In mice it blocks

cocaine-stimulated locomotion even at doses that are normally lethal. In rats CocH vector robustly eliminates cocaine-primed reinstatement of drug-seeking behavior (a model for addiction relapse in human users) and greatly reduces cocaine's reward value. In fact, our recent unpublished data show that a single vector treatment will abolish ongoing responding by rats working in operant chambers for cocaine reward delivered directly into the vena cava. This therapeutic effect persisted for the duration of a 10-week study. The CocH vector approach is now moving into studies in non-human primates, in preparation for eventual clinical trial. Considering the potential benefits as well as the hazards, we judge that systemic gene transfer of cocaine hydrolase, focused on reducing risk of relapse into drug-seeking after a period of abstinence, offers realistic potential for a significant advance in treating cocaine addiction.

Learning Objectives:

- Achieve a basic understanding of the potential effects on drug reward when a cocaine hydrolyzing enzyme is delivered by viral gene transfer.
- Gain a sense of the progress to date and the obstacles that remain in moving enzyme gene transfer therapy for cocaine abuse into phase I clinical trial.

Literature References:

- Geng L, Gao Y, Chen X, Hou S, Zhan C, Radic Z, Parks R, Russell SJ, Pham L, and Brimijoin S. Viral gene transfer of mutant mouse butyrylcholinesterase provides lifetime high-level enzyme expression and reduced cocaine responses without evident toxicity. PloS-One 2013, Jun 28;8(6)e67446dol 10137.pone.0067446. PMID 23840704
- Brimijoin S, Shen X, Orson F, and Kosten T. Prospects, promise and problems on the road to effective vaccines and related therapies for substance abuse. Expert Rev. Vaccines 12(3): 323-332, 2013. PMID 23496671

PANEL
9:00 AM – 10:30 AM

PANEL OVERVIEW:
RECOGNIZING AND TREATING CATATONIA ACROSS THE DIAGNOSTIC SPECTRUM: THE IMPACT OF NEW DSM-5 CLASSIFICATION

Georgios Petrides[1], Andrew Francis[2], Dirk M. Dhossche[3], Stanley N. Caroff[4]
[1]The Zucker Hillside Hospital, Northshore-LIJ Health System, [2]SUNY Stony Brook, [3]University of Mississippi Medical Center, [4]Philadelphia VA Med. Ctr./University of Pennsylvania

In the recently implemented DSM-5 there is a new independent classification of "catatonia not elsewhere classified" (299.98) while the older “catatonic schizophrenia” (295.2) has been abandoned. This is in recognition that catatonia, can be seen in multiple psychiatric and medical conditions independent of schizophrenia, the same way as psychosis or cognitive impairment. This new classification, which is in line with NIMH’s RDoC initiative, creates new opportunities to study the biological underpinnings of this condition allowing for more homogeneous populations in clinical trials, neuroimaging and genetic studies. This symposium aims to discuss catatonia recognition and treatment across the diagnostic spectrum and implications on future research. Catatonia is clearly under-recognized in psychiatric and medical patients. It is associated with significant morbidity and mortality and prompt recognition and appropriate treatment are essential. Catatonia is treated with high doses of benzodiazepines, barbiturates and/or electroconvulsive therapy (ECT). Management of the underlying psychiatric or medical

condition, when this is identifiable, is also important. Prompt recognition and treatment is essential as medical complications can be severe and life-threatening. Catatonic symptoms are seen in many conditions including affective disorders, schizophrenia, neuroleptic malignant syndrome, epilepsy, CNS infections, injuries and ischemia, and at times without an identifiable underlying disorder. A population of interest is children and adolescents where increased prevalence has been reported in first-break psychosis, autistic patients with intractable tics, aggression and/or self-injury, and pediatric patients diagnosed with the newly coined anti-NMDAR encephalitis. The various types of catatonic presentation among diagnostic categories, as well as recognition and quantification of symptoms using standardized rating scales, will be discussed. Emphasis will be given on the treatment of catatonia, it's underlying biology and implications for new drug development. Overall, this symposium will highlight the renewed interest in the catatonic syndrome which is now dissociated from schizophrenia in DSM-5 and the new opportunities for integrated research and treatment development in more homogeneous populations.

Learning Objectives:

- To recognize catatonia in various diagnostic categories of DSM-5 and medical conditions.
- To discuss implications of the new classification of catatonia on the management of the syndrome.

INDIVIDUAL ABSTRACT:
CATATONIA: VIDEO WORKSHOP ON RECOGNITION AND MANAGEMENT

Andrew Francis
SUNY Stony Brook

Catatonia is clearly under-recognized in psychiatric and probably also in medical patients. Standardized instruments such as the Bush-Francis Catatonia Rating Scale [BFCRS] aid recognition and monitoring of treatment. Catatonia is accompanied by significant morbidity and mortality, so treatment is essential, whether by addressing underlying medical and neurological illness or by targeted treatment with lorazepam and ECT. Medical complications of severe or prolonged catatonia will be reviewed. Clinical vignettes will be employed throughout this presentation and audience participation encouraged. Video vignettes of actual medical and psychiatric patients with catatonia before, during, and after treatment will be shown. Use of these videos with explanatory comments fosters experience using the BFCRS to improve detection and quantification of clinical features of catatonia.

Learning Objectives:

- To utilize the Bush-Francis Catatonia Scale to name and identify common catatonic signs.
- To recognize common and unusual catatonic motor behaviors in medical and psychiatric patients.

Literature References:

- Francis, A. Catatonia: Diagnosis, Classification and Treatment. Current Psychiatry Reports 12: 180-185, 2010.
- Bush, G., Petrides, G., Dowling, F., Fink, M. and Francis, A. Catatonia: I. Rating scale and standardized examination, Acta Psychiatrica Scandinavica 93: 129-136, 1996.

INDIVIDUAL ABSTRACT:
PEDIATRIC CATATONIA: REVIEW AND NEW VAGAL THEORY

Dirk M. Dhossche
University of Mississippi Medical Center

Catatonia is a severe, potentially life-threatening, but treatable condition that warrants prompt diagnosis and treatment. Recent studies support that catatonia may be more common in children and adolescents than previously thought, at least in selected diagnostic groups and when applying uniform assessments. A boost for the recognition of pediatric catatonia comes from changes in DSM-5 accommodating the diagnosis of catatonia in a wider range of disorders and weakening the link between catatonia and the major psychotic and affective disorders. The new category Unspecified Catatonia may be particularly useful to increase early recognition and appropriate treatment of pediatric catatonia and catatonia in autism spectrum disorders. Pediatric catatonia also develops in children and adolescents with concurrent medical conditions, psychotic and affective disorders, toxic states, autism spectrum disorders, developmental disorders, tic disorders, posttraumatic conditions, and miscellaneous syndromes such as Kleine-Levin Syndrome and Pervasive Refusal Syndrome. Benzodiazepines and ECT are underutilized in pediatric catatonia yet current experience supports these treatments as effective and safe interventions for pediatric catatonia, without any signs of ensuing neuropsychological impairment. There are several theories on the mechanism of catatonia. A new vagal theory of catatonia may be useful to find new treatments for pediatric catatonia. This presentation will contain a literature review, case-reports with video-footage, and explication of a vagal theory of catatonia in order to increase recognition, appropriate treatment, and research of pediatric catatonia.

Learning Objectives:

- To learn about the prevalence and comorbidity of catatonia in children and adolescents.
- To review the implications of changes in DSM-5 in the classification of catatonia for the diagnosis of catatonia in children and adolescents.

Literature References:

- Dhossche D, Goetz M, Gadzag G, Sienaert P: New DSM-5 category Unspecified Catatonia is a boost for pediatric catatonia. Neuropsychiatry 3(4), 401-410 (2013).
- Dhossche D, Wilson C, Wachtel L: Catatonia in childhood and adolescence: implications for the DSM-5. Prim Psychiatry 17, 35-39 (2010).

INDIVIDUAL ABSTRACT:
LONGITUDINAL ASSESSMENT OF THE PSYCHOMOTOR DIMENSION IN PSYCHOSIS: IMPLICATIONS FOR TREATMENT

Stanley N. Caroff
Philadelphia VA Med. Ctr./University of Pennsylvania

Although Kahlbaum proposed catatonia as a distinct disease entity, Kraepelin and Bleuler included catatonia among the schizophrenias, which remained the prevailing view until the rediscovery of catatonic symptoms in a broad range of mental and medical disorders. This led to the de-linking of catatonia from schizophrenia in DSM 5 in addition to the introduction of an unspecified category of catatonia. However, the longitudinal course of catatonia, considered critical by Kahlbaum, is not covered in DSM 5 but may represent an important component in the differentiation of psychomotor disorders with implications for treatment. Subsequent work by the

Gjessings on periodic catatonia and the classification system of the Wenicke-Kleist-Leonhard group provide a long-term perspective on psychomotor disorders and their treatment. Using this broader approach, this presentation will review the evidence on the acute and maintenance treatment of catatonic symptoms including use of benzodiazepines, ECT, lithium and anticonvulsants. Particular focus will be on critical examination of evidence on the efficacy, tolerability and toxicity of old and new antipsychotic drugs in patients with diverse psychomotor disorders including cycloid psychoses, periodic catatonia and the chronic systematic schizophrenias.

Learning Objectives:

- Participants will be able to differentiate among types of catatonic syndromes based on symptoms course and outcome.
- Participants will be able to discuss the evidence on acute and prophylactic pharmacological treatment of psychoses with catatonic symptoms.

Literature References:

- Tandon R, Heckers S, Bustillo J, et al. Catatonia in DSM-5. Schizophr Res 2013;150:26-30.
- Peralta V, Campos MS, de Jalon EG, et al. DSM-IV catatonia signs and criteria in first-episode, drug-naive, psychotic patients: psychometric validity and response to antipsychotic medication. Schizophr Res 2010;118:168-75.

PANEL
9:00 AM – 10:30 AM

PANEL OVERVIEW:
RESEARCH FORUM: MEDITATIVE PRACTICES, UNDERLYING NEUROBIOLOGICAL MECHANISMS, AND APPLICATION TO MENTAL HEALTH

Emmeline Edwards[1], Kristen Huntley[2], Kelvin O. Lim[3], Amishi Jha[4], Richard J. Davidson[5], David Shurtleff
[1]NIH, National Center for Complementary and Alternative Medicine (NCCAM), [2]NIH/NCCAM, [3]University of Minnesota, [4]University of Miami, [5]University of Wisconsin, Madison

Meditative and mindfulness-based approaches are being studied as potential non-pharmacological interventions for stress reduction, cognitive enhancement and for symptom management for a variety of medical conditions. The purpose of this panel is to describe (1) these meditative practices; how they are currently being used and evaluated, (2) the application of fMRI, PET, EEG, and other technology to understand the underlying neurobiological mechanisms and what is known about the impact on brain function, (3) a conceptual model of the possible mechanisms of action of meditation/meditative practices as clinical interventions, and (4) what is known about the effectiveness of meditative approaches for enhancing resilience, managing symptoms in psychiatric disorders, and improving cognition. Each presenter will describe their research addressing these topics. Overall, this symposium will highlight the possible mechanisms by which meditative practices mediate emotional and behavioral regulation. Meditative practices could complement conventional care and research studying possible mechanisms of action may lead to new treatment targets for psychiatric and other disorders. Gaps and opportunities for new and innovative research on meditative approaches, including future research needs, and the potential of combining this approach with other treatment modalities in the era of the National BRAIN Initiative will be discussed.

Learning Objectives:

- Session participants will be able to describe different types of meditative approaches, some of the indications for which interventions incorporating meditative approaches are being studied, and will learn what is currently known about the effectiveness of these approaches.
- Session participants will learn about technologies that are being used to study potential mechanisms of action of meditative interventions and the effect of these meditative approaches on human brain function.

INDIVIDUAL ABSTRACT:
NEUROIMAGING AS A TOOL FOR THE STUDY OF MEDITATION

Kelvin O. Lim
University of Minnesota

Advances in neuroimaging techniques have provided investigators with new tools for studying the brain. While much work has been focused on pathological conditions, there has been increasing interest in examining how the brain is altered by ancient practices such as meditation. Magnetic resonance can provide a broad range of information about the brain including: anatomical, chemical, tissue microstructure and connectivity; Positron Emission Tomography can provide information about metabolism and receptors. Such information will be important in helping to better understand how various types of meditation alter the brain and how they might be helpful as a therapeutic intervention for clinical problems. Work from our current projects in meditation for the treatment of PTSD will also be presented.

Learning Objectives:

- To describe three types of information that neuroimaging can provide.
- To describe what brain alterations might be expected following different meditation practices.

Literature References:

- Bassett DS, Nelson BG, Mueller BA, Camchong J, Lim KO. Altered resting state complexity in schizophrenia. Neuroimage. 2012 Feb 1;59(3):2196-207.
- Johnson MD, Lim HH, Netoff TI, Connolly AT, Johnson N, Roy A, Holt A, Lim KO, Carey JR, Vitek JL, He B. Neuromodulation for brain disorders: challenges and opportunities. IEEE Trans Biomed Eng. 2013 Mar;60(3):610-24.

INDIVIDUAL ABSTRACT:
WHAT IS KNOWN ABOUT THE EFFECTIVENESS OF MEDITATIVE APPROACHES FOR RESILIENCE AND COGNITIVE ENHANCEMENT?

Amishi Jha
University of Miami

This talk will provide an overview of recent neuroscientific findings regarding the effectiveness of meditative training to promote resilience and cognitive enhancement. A large and growing literature finds that stress degrades cognitive functions and weakens the capacity to regulate emotions. Further, chronic stress may lead to cognitive failures and psychological illness. Meditative training may build core cognitive and emotion-regulation processes to protect against this degradation and promote resilience. Findings from a broad range of high stress cohorts will be discussed, including military service members, teachers, students, as well as incarcerated youth. These studies report that attention, working memory, and mood improve, and mind-wandering is curbed with mindfulness meditation training. Together, these findings suggest that

psychological resilience can be bolstered via meditative training offered to high stress cohorts who are most vulnerable to psychological dysfunction and disease.

Learning Objectives:

- To understand how cognitive systems are evaluated using brain imaging and behavioral methods.
- To understand the how attention, working memory, and mind-wandering are altered by meditation practices.

Literature References:

- Jha, A.P., Stanley, E.A., Kiyonaga, A., Wong, L., & Gelfand, L. (2010). Examining the Protective Effects of Mindfulness Training on Working Memory and Affective Experience. Emotion, 10(1), 54–64.
- Baijal, S., Jha, A. P., Kiyonaga, A., Singh, R., & Srinivasan, N. (2011). The Influence of Concentrative Meditation Training on the Development of Attention Networks during Early Adolescence. Frontiers in Developmental Psychology. 2(153): 1-9.

INDIVIDUAL ABSTRACT:
INNOVATION AND OPPORTUNITIES IN NEUROSCIENTIFIC RESEARCH ON MEDITATION

Richard J. Davidson
University of Wisconsin, Madison

With Thalidomide we learnt that drugs can be potent teratogens and increase orders of magnitude the risk of specific malformations in fetuses exposed early in pregnancy. Afterward, scientific controversy led to the discontinuation of one of the best studied, and most likely safe, drugs in pregnant women: Bendectin. Since then, the evaluation of drug teratogenicity in humans has been marked by a fear to both under and over-reaction to findings. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy. SSRI use late in pregnancy has been associated with several adverse perinatal outcomes including prematurity and neonatal withdrawal. Initial studies on the use of SSRIs early in pregnancy had reported no meaningful association with congenital malformations. However, in 2005, the US Food and Drug Administration (FDA) warned healthcare professionals that early prenatal exposure to paroxetine may increase the risk of congenital cardiac malformations. Since then, there has been an exponential increase in the number of studies published on this topic; followed by a larger number of reviews and opinion pieces. Some studies found significant associations between antidepressants and major congenital malformations and others did not. Based on the same original findings, some experts conclude evidence of harm and others evidence of safety. The issue of whether paroxetine in particular, or SSRIs in general, does in fact increase the risk for cardiovascular malformations remains unresolved. It is unclear whether the reported associations are causal (attributable to teratogenic effects of specific drugs), or due to systematic error (e.g., confounding by underlying depression) or chance in the context of multiple comparisons. On the other hand, the reported lack-of-association may be due to misclassification of exposure (e.g., non-compliance with prescriptions) or outcome (e.g., inaccurate diagnoses), or to inadequate statistical power. In this session, we will conduct an autopsy on the discrepant findings on SSRIs teartogenicity and discuss the final diagnosis: Thalidomide or Bendectin.

Learning Objectives:

- To understand the major differences among different styles of meditation practice.
- To understand the brain circuits that are shaped by different types of meditation practices.

Literature References:

- Davidson, R. J. & McEwen, B. S. (2012). Social influences on neuroplasticity: Stress and interventions to promote well-being. Nature Neuroscience 15(5), 689-95.
- Lutz, A., Slagter, H. A., Dunne, J., & Davidson, R. J. (2008). Attention regulation and monitoring in meditation. Trends in Cognitive Sciences 12(4), 163-169.

PANEL
9:00 AM – 10:30 AM

PANEL OVERVIEW:
RISKS POSED BY DUPLICATE OR INAPPROPRIATE SUBJECTS IN CLINICAL TRIALS AND METHODS FOR MITIGATING THE RISK

Jonathan Rabinowitz[1], Michael Detke[2], Ellis Wilson[3], Janet Williams[4]
[1]Bar Ilan University, [2]Indiana University, [3]AstraZeneca Pharmaceuticals, [4]MedAvante, Inc.

The purpose of this panel is to understand the risks to signal detection posed by duplicate patients in clinical trials and to learn about methods for mitigating the risks of duplicate patients. Data will be presented on apparently duplicate patients in CATIE and STAR*D and on duplicate patients enrolled in a large development program in depression and the strategy used by the team to identify and prevent subjects from enrolling in more than one study within the program. Data will also be presented on how removing duplicate patients in another trial resulted in improved signal detection on a primary outcome measure which became statistically significant after removing duplicate patients. The duplicate patient phenomena will be examined also in the larger context of protocol non-adherence and the "professional" patient who may be more likely to inflate initial severity, downplay potentially disqualifying comorbidities and exaggerate treatment responses. Finally a free web based initiative open to all sponsors to use to screen for duplicate patients, both at time of screening, and for completed studies, using historical data, will be presented. This initiative identifies apparent duplicate patients within and across sponsors and therapeutic areas and helps prevent enrolling duplicate subjects in studies.

Learning Objectives:

- Understand the risks posed by duplicate patients in clinical trials.
- Learn about methods for mitigating the risks of duplicate patients.

INDIVIDUAL ABSTRACT:
EVIDENCE AND RISKS OF DUPLICATE SUBJECTS IN CLINICAL TRIALS AND HOW YOU CAN MINIMIZE THE RISK

Jonathan Rabinowitz
Bar Ilan University

Participation of subjects concurrently enrolled in another study, or the same study more than once, could severely bias study results. Even a small number of duplicate subjects can lead to a negative or failed trial. Effect sizes of many drugs are small making such studies particularly sensitive to duplicate subjects and other measurement error. Data will be presented from a depression trial showing how 8 out of 150 placebo patients, simultaneously receiving active

treatment in another trial, would be sufficient to lead to a negative study and how the removal of 5 pairs of matches changed the results in another study yielding statistically significant results. In addition data will be presented showing that 42 subjects in CATIE (n=1460) appear to have been duplicates within the study as they matched on eight key demographic variables (29 of them had one match, 7 had two and two had 3, representing 87 patients) and 103 subjects in STAR*D (n=4042) as they matched on eight key demographic variables (96 of them had one match, 7 had 3, representing 213 patients). Simulations (n=100,000) and actual birth cohort data (n=92,000) suggest that the likelihood of false matches with these matching variables for CATIE were less than 7% and in STAR*D less than 5%. Data on optimal matching variables will be presented showing that a few select demographic variables are sufficient to yield matches with high certainty. Finally, a free online tool, DupCheck.org will be presented which allows for identifying apparent duplicate subjects within and across studies and sponsors. The site can be used at time of screening and can also be used for sensitivity analysis of completed studies. DupCheck uses doubly encrypted de-identified data and works by comparing encrypted data, making it HIPAA compliant. The results presented on CATIE and STAR*D are probably only a portion of the actual duplicate subjects in those studies. Additional duplicates would probably have been revealed were enrolment in other concomitant studies to have been checked using a system like DupCheck which is a cross sponsor system covering a wide spectrum of trials not exclusively CNS.

Learning Objectives:

- Participants will understand the risks of trial failure associated by participation of duplicate subjects.
- Participants will learn about a collaborative effort in CNS and across medicine to reduce participation of duplicate subjects.

Literature References:

- Brody, B., Leon, A. C., & Kocsis, J. H. (2011). Antidepressant clinical trials and subject recruitment: just who are symptomatic volunteers? Am J Psychiatry, 168(12), 1245-1247. doi: 10.1176/appi.ajp.2011.11060864
- Rabinowitz, J. (1998). A method for preserving confidentiality when linking computerized registries. Am J Public Health, 88(5), 836.

INDIVIDUAL ABSTRACT:

THE PROFESSIONAL PATIENT 'SPECTRUM' OR SIMPLY INAPPROPRIATE PATIENTS: 50 SHADES OF GREY IN PROTOCOL NON-ADHERENCE

Michael Detke

Clinical Professor of Psychiatry, Indiana University

Even with well-intentioned volunteer study subjects and clinical trial personnel, many opportunities exist for various forms of protocol non-adherence. We will explore some of these areas and bring to bear recent data that address the nature and magnitude of some problems. One clear area for concern is in subject selection. Recent data have shown that many subjects may not meet all inclusion/exclusion criteria. At least three important aspects of subject selection have been studied across several modalities: Initial diagnosis, disease severity and concomitant or recent enrolment in another study. For example, Sachs, et al. (2012) showed that nearly 2/3 of subjects did not meet at least 1 protocol-specified eligibility criterion on the basis of computer assessments in an adjunctive trial of ziprasidone in acute mania. The authors speculate that

enrollment of ineligible subjects may contribute to trial failure. Likewise, Detke, et al. (2010) found that 1/4 - 1/2 of subjects may not meet protocol-specified diagnostic criteria, and over 1/3 may not have met criteria for initial severity, in a number of studies employing remote, independent, blinded raters to review these criteria. Debrota, et al. (1999) and others have shown similar results on initial severity with computer ratings following clinician assessments. Other presenters in the session will share data on concomitant enrolment. While some subjects may meet all of the protocol inclusion and exclusion criteria technically, and at the screening visit, they may not continue to do so, or to comply with all protocol requirements. It is almost certainly the case that patient self-report of compliance (e.g., taking study drug; reporting adverse events) is less than perfect. There is a well-documented literature on demand characteristics which indicates that subjects bias their reporting in the direction which they believe the questioners would like to hear - especially questioners in positions of authority (like doctors). However, it is hard to assess the degree of bias. One area in which we can assess this is in study drug compliance using pK data. Older studies have shown that using pK to define a compliant population for post-hoc analysis can be valuable in POC, as in the duloxetine development program, and some new data from recent MDD studies show that up to 1/4 of patients randomized to drug had undetectable levels at one or more study visits. Lastly, again with even well-intentioned subjects and questioners there are human biases. Therapeutic alliances are formed, and expectation of improvement over the course of treatment influences the responses to questions in a systematic way. This too can be viewed as non-adherence in a broad sense. All of these areas - subject selection, protocol compliance, and expectation bias - can influence placebo response and signal detection. We need to be mindful of these influences and design/implement our trials thoughtfully regarding them to optimize the scientific outcomes. Specific protocol development guidelines will be presented to help minimize these risks.

Learning Objectives:

- While some subjects may meet all of the protocol inclusion and exclusion criteria technically, and at the screening visit, they may not continue to do so, or to comply with all protocol requirements.
- The above non-adherence may have significant impact on placebo response, and signal detection in such clinical trials.

Literature References:

- The Challenge of Subject Selection in Clinical Trials: New Data. (Detke MJ, Williams JBW, Kobak KA, Ellis A, Giller E, Brown B, De Santi S, Reines S, Kane JM). New Clinical Drug Evaluation Unit 50th Annual Meeting, Boca Raton FL (June 2010)
- Sachs GS, et al. Adjunctive Oral Ziprasidone in Patients with Acute Mania Treated with Lithium or Divalproex, Part 2: Influence of Protocol-Specific Eligibility Criteria on Signal Detection. J Clin Psychiatry. 2012 Nov;73(11):1420-5

INDIVIDUAL ABSTRACT:
PROVEN STRATEGIES TO MITIGATE THE RISK OF ENROLLING PROFESSIONAL SUBJECTS IN LARGE DEPRESSION STUDIES

Brooke Geibel
Shire

The discovery and development of meaningful new medicines is a complex, costly and inherently risky undertaking. Robust late-stage pharmaceutical research is dependent upon

appropriate patients and the compliance of those patients with clinical study protocols. Conversely, inappropriate noncompliant patients in clinical trials represent a risk to pharmaceutical research and to the patients this research is intended to serve. Unfortunately, a number of factors have recently converged to create an environment where inappropriate, noncompliant clinical trial participants are not uncommon. Investigators commonly refer to these participants as 'professional patients' or sometimes 'ATM patients.' Late stage clinical trials generally need to establish evidence for both safety and efficacy. Reasonably large numbers of patients are required to establish efficacy and safety with confidence. Business pressures to reduce time to market instill a sense of urgency in development teams and investigative sites. Competitive pressures at the site level create an environment where financial incentives for patients are standard. These financial incentives encourage clinical trial participation by both bona fide, appropriate patients and inappropriate, noncompliant patients. CNS studies and other areas of research where inclusion criteria and endpoint measures are subjective or 'soft' are particularly vulnerable to this manipulation by inappropriate, noncompliant patients who are not sincere about complying with study protocols. Investigative sites and research teams recognizing this risk may employ a number of different tactics to discourage and/or identify noncompliant patients before they undermine clinical trial results. This presentation will detail the following suite of strategies applied in a recent depression program: • Use telephone interviews conducted by expert psychiatrists to validate the diagnosis and patient appropriateness• Reduce ceiling for remuneration• Validate compliance via blood levels during run-in period• Analyze concordance between investigator administered HAM-D and patient rated HAM-D. These strategies combined to reduce the percentage of professional subjects from levels as high as 20% to less than 5% in each of the four pivotal studies in this program. Failure to recognize, prevent and/or mitigate this abuse has serious consequences. Funding for research is not unlimited, so every dollar invested to mitigate risks posed by professional subjects is a dollar that can't be invested in researching another compound to help another group of patients. But perhaps the greatest cost is the potential for unreliable research results - and here the costs are tallied in years of research wasted, and potential missed opportunities to help improve the lives of thousands of patients who might otherwise benefit from a new medication. Our awareness of this behavior and our concerted efforts to limit and extinguish it will go a long way to preserving the next generation of meaningful medicines.

Learning Objectives:

- Learn to recognize key characteristics of professional patients.
- Learn strategies that can be implemented to reduce enrollment of professional patients.

Literature References:

- Brody, B., Leon, A. C., & Kocsis, J. H. (2011). Antidepressant clinical trials and subject recruitment: just who are symptomatic volunteers? Am J Psychiatry, 168(12), 1245-1247. doi: 10.1176/appi.ajp.2011.11060864
- The Failed CNS Studies Phenomenon: Is the Final Factor Looking Us Right in the Eye? Charles S. Wilcox*, Judy L. Morrissey, Nader Oskooilar, Mellissa M. Henry, Daniel E. Grosz, My-Linh Tong, Don F. De Francisco. Neuropsychopharmacology (2012) 38, S314–S446. doi:10.1038/npp.2012.221

PANEL
10:45 AM – 12:15 PM

PANEL OVERVIEW:
DIMENSIONAL SYMPTOM AND DISABILITY MEASURES IN DSM-5
William Narrow[1], Eve K. Mościcki[1], Diana E. Clarke[1], Lori L. Davis[2]
[1]American Psychiatric Association, [2]University of Alabama School of Medicine
With the identified limitations of categorical diagnostic systems intersecting with increasing adoption of measurement-based care and patient-reported outcomes (PROs), the fifth revision of DSM (DSM-5) advocated for further investigation of dimensional assessment measures. Age-specific patient-reported symptom measures that cut across diagnoses, referred to as cross-cutting measures, and the World Health Organization Disability Assessment Schedule for the assessment of disabilities are now contained in Section III of DSM-5. The systematic measurement of common cross-cutting symptoms and disabilities has the potential not only to help clinicians in documenting and justifying diagnostic and treatment decisions but also to increase patient involvement in these decisions. This symposium will provide data on clinical utility, psychometric properties, and associations with diagnosis for these patient-reported dimensional measures, based on the findings from the DSM-5 Field Trials conducted in large academic centers and routine clinical practices, in both adult and child populations. The Field Trials highlight the potential use of PROs to enhance measurement-based care, which has implications for the future of diagnostic and treatment outcome assessment. This is important given recent changes in the U.S. health care system and subsequent emphasis on evidence-based medicine and patient-centered care.

Learning Objectives:
- Identify the patient-reported dimensional measures proposed for the DSM -5.
- Provide examples of how the DSM-5 patient-reported dimensional measures in clinical settings demonstrated feasibility and clinical utility in the DSM-5 field tests.
- Describe the relationships between disability, as measured by the World Health Organization Disability Assessment Schedule, and diagnoses given by clinicians in child and adult populations.

INDIVIDUAL ABSTRACT:
DSM-5 CROSS-CUTTING DIMENSIONAL MEASURES: RELIABILITY, SENSITIVITY TO CHANGE, AND ASSOCIATION WITH DISABILITY
Diana E. Clarke
American Psychiatric Association
Patients' reports of their symptoms during routine clinic visits have significant impact on diagnosis, treatment, and follow-up care. The Work Groups involved in the Fifth Revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) have proposed age-specific patient-rated cross-cutting measures to better assess and track patients' symptom presentations. Using a multi-site test-retest reliability study with stratified random sampling, we examined the feasibility, clinical utility, reliability, and sensitivity to change of the adult version of the measures. Intraclass correlation coefficients for stratified samples and their bootstrap 95% confidence intervals, using SAS and SUDAAN, were calculated for each measure. Weighted linear regression and correlation analyses were used to examine sensitivity to change. Items on the DSM -5 patient-rated cross-cutting measures mostly fell in the good-to-excellent range for

ICC. Patients' ratings of symptom severity were significantly related to their ratings of disability at baseline and over time. Patients found the measures easy to use and informative to their clinicians. Clinicians found the measures clinically useful and easy to incorporate in their assessment of the patient. These results provide some evidence of the feasibility of incorporating patient-rated measures into busy clinic practices.

Learning Objectives:

- Understand how clinical utility, reliability, and feasibility of cross-cutting symptoms were assessed in the DSM-5 Field Trials in routine clinical settings.
- Be able to name some examples of findings from the DSM-5 Field Trials in large academic settings that demonstrated patients' opinions and perspectives on the DSM-5 cross-cutting measures.

Literature References:

- Clarke DE, Narrow WE, Regier DA, Kuramoto SJ, Kupfer DJ, Kuhl EA, Greiner L, Kraemer HC. DSM-5 field trials in the United States and Canada, Part I: study design, sampling strategy, implementation, and analytic approaches. Am J Psychiatry. 2013 Jan 1;170(1):43-58.
- Narrow WE, Clarke DE, Kuramoto SJ, Kraemer HC, Kupfer DJ, Greiner L, Regier DA. DSM-5 field trials in the United States and Canada, Part III: development and reliability testing of a cross-cutting symptom assessment for DSM-5. Am J Psychiatry. 2013 Jan 1;170(1):71-82.

INDIVIDUAL ABSTRACT:

DSM-5 DIMENSIONAL SYMPTOM AND DISABILITY MEASURES IN ROUTINE CLINICAL PRACTICE SETTINGS

Eve K. Mościcki

American Psychiatric Association

This study examined the feasibility and clinical utility of patient-rated, cross-cutting measures in the DSM -5 Field Trials in Routine Clinical Practice Settings, and the association of levels of symptom severity with DSM -5 diagnoses and levels of disability on the World Health Organization Disability Assessment Schedule 2.0 (WHODAS II). Patients completed structured assessments of cross-cutting psychiatric symptom domains and the WHODAS II. Clinicians conducted a diagnostic interview and completed diagnostic and other measures. Adult patients' ratings of symptom severity were consistently related to their clinician-assigned primary DSM -5 diagnosis. Overall mean scores on the patient-rated WHO-DAS II were highest for adult patients with clinician-assigned DSM -5 diagnoses of bipolar and related disorders and any depressive disorders. Child patients' or parent ratings of symptom severity within symptom domains were chiefly related to clinicians' primary DSM-5 diagnoses for internalizing disorders, regardless of the symptom domain. Overall mean scores on the WHODAS II rated by children 11-17 years and parents of children 6-11 years were highest for patients with clinician-assigned DSM-5 diagnoses for disorders other than internalizing or externalizing conditions. Parent-rated WHODAS II scores for children 6-11 years were highest for patients with clinician-assigned DSM-5 diagnoses of internalizing disorders. Both patients and clinicians found the measures easy to use and informative.

Learning Objectives:

- To describe the general feasibility and clinical utility of using the DSM-5 patient-reported measures in routine clinical settings.

- To provide examples of findings from the DSM-5 Field Trials in Routine Clinical Practice Settings that demonstrate the relationship between patient-rated symptom severity levels and clinician-assigned diagnoses.
- List some specific ways the results the DSM-5 Field Trials in Routine Clinical Practice Settings demonstrate the relationship between patient-rated symptom severity levels and disability levels.

Literature References:

- Mościcki EK, Clarke DE, Kuramoto SJ, Kraemer HC, Narrow WE, Kupfer DJ, Regier DA. Testing DSM-5 in routine clinical practice settings: Feasibility and clinical utility. Psychiatr Serv 2013; 64(10):952-60.
- Narrow WE, Clarke DE, Kuramoto SJ, Kraemer HC, Kupfer DJ, Greiner L, Regier DA. DSM-5 field trials in the United States and Canada, Part III: development and reliability testing of a cross-cutting symptom assessment for DSM-5. Am J Psychiatry. 2013 Jan 1;170(1):71-82.

INDIVIDUAL ABSTRACT:

THE WORLD HEALTH ORGANIZATION DISABILITY ASSESSMENT SCHEDULE IN THE DSM-5 FIELD TRIALS: ASSOCIATIONS WITH PSYCHIATRIC DIAGNOSIS

William Narrow

American Psychiatric Association

This study examined the association of clinician-assigned DSM-5 diagnoses with mean disability scores from the patient-reported WHODAS in the DSM-5 Field Trials. The field trials were a multi-site test-retest reliability study: seven sites with adult patient populations and four sites with child and adolescent populations. Consecutive patients at each site were screened and stratified into groups based on their DSM-IV diagnoses. For the test and retest visits, patients completed a set of self-administered symptom and disability measures before meeting with the clinician. Adult patients completed the WHODAS. For the child field trials, a newly developed disability measure based on WHODAS items was completed by parents of all children ages 6-17 and children ages 11 and over. Results were sent electronically to the clinician prior to the clinical evaluation. Weighted analyses using SAS and SUDAAN software were conducted. To estimate reliability, intraclass correlation coefficients for stratified samples and 95% confidence intervals were calculated. Mean disability scores were calculated for diagnoses made at the first visit. Mean scores for patients with one diagnosis and for two or more diagnoses were also compared. Adult patients with major depressive, anxiety, or stress-related disorders reported the highest mean disability levels. Patients with psychotic, neurocognitive, or bipolar disorders tended to report lower disability than the other disorders. Patients with disorders "not elsewhere classified" had significantly lower disability scores, and patients with one disorder had lower scores than patients with two or more disorders. Older children with autism spectrum disorder had the highest disability levels (by parent report), while parents of younger children reported the highest levels of disability for patients with major depressive disorder. Parents of the older children consistently reported higher disability levels than their children. The use of a disability measure separate from symptom assessment can help clinicians develop more comprehensive treatment plans and provide additional justification for treatment decisions. It also can serve as a common language for clinicians, much as the DSM diagnostic criteria helped provide a common diagnostic language. The results of this study provide directions for further research into the developmental aspects of disability and differences in self-reported information by patients who may have cognitive deficits.

Learning Objectives:

- Explain the disability domains of the WHODAS and their use in the DSM-5 Field Trials.
- Describe how WHODAS scores varied according to the diagnoses and ages of the patients in the DSM-5 Field Trials.

Literature References:

- Narrow WE, Kuhl EA. Clinical significance and disorder thresholds in DSM-5: The role of disability and distress. In: The Conceptual Evolution of DSM-5. Regier DA, Narrow WE, Kuhl EA, Kupfer DJ (eds). Arlington, VA: American Psychiatric Association, 2011.
- Üstün TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, Saxena S, von Korff M, Pull C, and in collaboration with WHO/NIH Joint Project. Developing the World Health Organization Disability Assessment Schedule 2.0 Bulletin of the World Health Organization 2010;88:815-823.

PANEL
10:45 AM – 12:15 PM

PANEL OVERVIEW:
NIAAA SPONSORED ACTIVE UPDATE: MISSING DATA IN ALCOHOL USE DISORDER CLINICAL TRIALS - ISSUES AND ANALYTIC METHODS

Raymond F. Anton[1], Robert L. Stout[2], Per Sorensen[3], Katie Witkiewitz[4], Raye Z. Litten[5]
[1]Medical University of South Carolina, [2]Pacific Institute for Research and Evaluation, [3]H. Lundbeck A/S, [4]University of New Mexico, [5]NIAAA

In alcohol use disorder clinical trials the main outcome of importance is self-reported alcohol consumption (drinking) over the course of the trial. State of the art collection involves a calendar method whereby individuals report their daily drinking amounts on a period basis. However, given the nature of the disease, for various reasons trial participants often do not fully report their drinking and often drop out of treatment and follow-up leaving considerable missing drinking data in the final analysis. This session under the auspices of the Alcohol Clinical Trials Network (ACTIVE) and NIAAA will overview the extent of missing data, its causes, and analytic methods, including various data imputation methods, to aid validity and interpretation of trial results for both clinical and regulatory purposes. Dr. Anton will present a brief overview of the ACTIVE mission and goals and then provide a overview of missing drinking data in clinical trials, its extent, causes, and methods to reduce the amount of missing drinking data. Dr. Stout will show data from the large US NIAAA funded COMBINE Study in which he evaluated the extent of drinking before and after treatment dropout. These data will assist in decisions about missing drinking data assumptions as well as suggest opportunities to reduce treatment dropout and missing data. Dr. Per Sorensen will present analytic methods applied during presentation of clinical trial results to the European Medicines Agency (EMA) during recent approval of nalmfene for alcohol dependence. He will show various imputation strategies for missing drinking data and how these strategies affected clinical trial interpretation and significance. Dr. Katie Witkiewitz will show data evaluating various analytic methods to compensate for missing drinking data in the COMBINE Study and also how the imputation methods used in the nalmefene regulatory review could be applied to the US COMBINE Study data. Dr. Litten will lead a discussion on the importance of developing a consensus on best practices of handling missing data in alcohol use disorder trials, the importance of minimizing missing drinking data, and how analytic methods and validity can be improved. The assumption is that similar ideas and

methods could be applied to results in clinical trials of various other disorders where study non-completion rates are high and missing data imputation methods and analysis are required..

Learning Objectives:

- To appreciate the role and causes of missing alcohol consumption data in alcohol use disorder clinical trials.
- To better understand how to avoid missing alcohol consumption data and when present the range of analytic and imputation methods to estimate true values for the missing data.

INDIVIDUAL ABSTRACT:

OVERVIEW OF THE ACTIVE WORKGROUP AND MISSION AND IMPORTANCE OF MISSING DRINKING DATA IN ALCOHL USE DISORDER TRIALS

Raymond F. Anton
Medical University of South Carolina

The Alcohol Clinical Trials Initiative Workgroup (ACTIVE) works under the sponsorship of the ASCP to foster a consensus on best methods for alcohol use disorder clinical trials. This small workgroup, sponsored by the pharmaceutical industry, bring expert academics, government agencies (NIAAA, NIDA, FDA, EMA), and pharmaceutical companies, together to discuss important questions and issues related to clinical trials for alcohol dependence. The ultimate goal is, through data based information, to improve scientific methods and ultimately provide consensus guidance toward regulatory pathways for approval of medications for the treatment the socially costly, and individually debilitating, alcohol use disorders. By consensus of the ACTIVE members, one of the top six questions/concerns relates to missing drinking data in clinical trials. In alcohol dependence clinical trials of 3 to 6 months duration drop outs from study participation range from 30-50% respectively. Since the unit of measure is daily alcohol consumption (captured by a calendar based collection method) this high study dropout rate translates into considerable missing daily drinking data. It has been unclear how to account for and possibly impute this missing drinking data. All imputation methods and assumptions lead to biased estimates. For instance, one cannot assume that drinking occurring before drop out is reflective of drinking after study drop out. Indeed, most experts believe that the main reason for study drop out is related to "relapse drinking" rather than "sustained improvement". On the other hand, data suggests that assuming drinking has returned immediately to pre-randomization levels is too conservative and unwarranted. Since all estimates of missing drinking data are inherently biased, the consensus of ACTIVE is that missing drinking data should be avoided and prevented. In fact, in the 4 month COMBINE Study, the largest pharmacotherapy trial ever conducted by NIAAA (n=1383), even though the dropout rate was about 40%, with very aggressive management missing drinking data was only about 6%. This was obtained by 1) maintaining contact with study dropouts and providing expectations that they should provide end of study (week 16) drinking data 2) incentivizing return for the end of study appointments 3) collecting drinking data over the phone prior to subject final visit 4) expecting, empowering, and monitoring research staff in the collection of missing drinking data and 5) allowing a wide window (up to 2 months) post final visit to retrospectively collect historical drinking data. Despite study protocol best efforts and practice, missing drinking data will need to be dealt with in efficacy analyses. Imputation of missing data can take several forms, including imputing the following for each missing drinking assessment day: 1) pre-drop out drinking level 2) a heavy drinking day 3) individual pre-randomization drinking level 4) mean of the total drug group drinking level at each follow-up point 5) estimates of drinking based on a priori parameters

derived from other "like" subjects 6) the placebo group drinking level for all missing drinking data days. This discussion will introduce the concepts dealt with in subsequent presentations.

Learning Objectives:

- To appreciate the goals of the Alcohol Clinical Trials Initiative and how it's mission will advance and standardize methods for clinical trials in alcohol dependence and regulatory pathways.
- To better understand the causes of missing drinking data in alcohol clinical trials and how to reduce the amount of missing drinking data.

Literature References:

- Anton RF, Litten RZ, Falk DE, et al. The Alcohol Clinical Trials Initiative (ACTIVE): Purpose and Goals for Assessing Important and Salient Issues for Medications Development in Alcohol Use Disorders. Neuropsychopharmacology. Jan 2012;37(2):402-411.
- Anton RF, Randall CL. Measurement and choice of drinking outcome variables in the COMBINE Study. Journal of Studies on Alcohol - Supplement. Jul 2005(15):104-109; discussion 192-103.

INDIVIDUAL ABSTRACT:
HOW DOES DRINKING CHANGE WHEN PEOPLE STOP TAKING MEDICINES DURING A CLINICAL TRAIL? - IMPLICATIONS FOR MISSING DRINKING DATA REDUCTION AND IMPUTATION

Robert L. Stout
Pacific Institute for Research and Evaluation

Aims: We used intensive longitudinal data methods to illuminate dynamic processes affecting patients' choices to stop medications within an alcohol treatment study. Previous work has focused on broad measures of medication adherence whereas we focus on dynamic changes in drinking both before and after patients stop medication. A secondary aim was to shed light on alternative methods of dealing with missing follow-up data in such studies. A better understanding of these processes should improve imputation methods and sensitivity analyses. Design: We conducted a secondary analysis of data from the COMBINE study, focusing on participants who stopped taking medications prior to the planned end of treatment. Using hierarchical linear modeling, we analyzed drinking in the weeks before and after medication usage stopped, and also studied longer-term outcomes at the end of COMBINE follow-up. Participants: We describe the sub-sample of COMBINE participants who stopped medications, and compare them to other participants. Measurements: The primary outcomes were percent of days abstinent and percent of heavy drinking days. Medication adherence data were used to estimate time to final medication dose. Findings: For many patients, an increase in drinking starts weeks before medications stop and drinking continues to increase afterwards. Variations are seen depending on when and why medications were stopped. Conclusions: The decision to stop medications appears to take place during a weeks-long process of disengagement from treatment, providing a window of opportunity for clinical intervention. These data also have important implications for treatment research methodology.

Learning Objectives:

- Participants will learn the implications of different research follow-up methods and missing data approaches for alcohol clinical trials.

• Participants will learn about factors that affect clients' decisions to stop medications, and how these factors affect future drinking.

Literature References:

• Panel on Handling Missing Data in Clinical Trials; National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials: The National Academies Press; 2010.

• Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. JAMA: The Journal of the American Medical Association. 2006;295(17):2003-17.

INDIVIDUAL ABSTRACT:

THE USE OF PATTERN MIXTURE MODELS FOR IMPUTATION AND ANALYSIS OF MISSING DRINKING DATA IN NALMFENE TRIALS FOR ALCOHOL DEPENDENCE DURING REGULATORY APPROVAL IN EUROPE

Per Sorensen

H. Lundbeck A/S

This talk will look at some of the single and multiple imputation methods used to handle missing data in the pivotal nalmefene efficacy studies designed to evaluate reduction of alcohol consumption in patients with alcohol dependence. Particularly, the use of Pattern Mixture Models will be introduced as a flexible framework for exploring different missing-not-at-random assumptions for the missing data within a repeated measurement analysis approach. The talk will show how different assumptions affect the estimates of the treatment effect and provide examples on how the assumptions behind the Pattern Mixture Models can be illustrated graphically so clinicians can judge the plausibility of the assumptions about the missing data

Learning Objectives:

• Application of Pattern Mixture Models in Alcohol Dependence Trials.

• Interpretation of results from trials with a non-negligible proportion of missing data.

Literature References:

• van den Brink et al. Efficacy of as-needed Nalmefene in Alcohol Dependent Patients with at least a High Drinking Risk Level: Results from a Subgroup Analysis of Two Randomised controlled 6-month studies. Alcohol alcoholism 2013;48(5):570–578

• Little RJ et al. The Prevention and Treatment of Missing Data in Clinical Trials. N Engl J Med 2012;367(14):1355-60.

INDIVIDUAL ABSTRACT:

VALIDITY OF VARIOUS MISSING DRINKING DATA IMPUTATION METHODS - RESULTS FROM RE-ANALYSIS OF THE US COMBINE STUDY

Katie Witkiewitz

University of New Mexico

Background: The rate of participant attrition in alcohol clinical trials is often substantial and can cause significant issues with regard to the handling of missing data in statistical analyses of treatment effects. It is common for researchers to assume that missing data is indicative of participant relapse and under that assumption many researchers have relied on setting all missing values to the worst case scenario for the outcome (e.g., missing=heavy drinking). This sort of

single imputation method has been criticized for producing biased results in other areas of clinical research, but has not been evaluated within the context of alcohol clinical trials and many alcohol researchers continue to use the missing=heavy drinking assumption. Methods: Study 1: Data from the COMBINE study, a multisite randomized clinical trial, were used to generate simulated situations of missing data under a variety of conditions and assumptions. We manipulated the sample size (n = 200, n = 500, and n = 1000) and dropout rate (5%, 10%, 25%, 30%) under three missing data assumptions (missing completely at random, missing at random, missing not at random). We then examined the association between receiving naltrexone and heavy drinking during the first 10 weeks following treatment using five methods for treating missing data (complete case analysis, last observation carried forward, missing=heavy drinking, multiple imputation, and full information maximum likelihood). Study 2: In a second set of analyses we used the full COMBINE dataset to examine results of last observation carried forward, baseline observation carried forward, missing=heavy drinking, multiple imputation, and pattern mixture models on the average effect of naltrexone on drinking trajectories during and following treatment. Results: Complete case analysis, last observation carried forward, and missing=heavy drinking produced the most biased naltrexone effect estimates and standard errors under conditions that are likely to exist in randomized clinical trials. Multiple imputation and maximum likelihood produced the least biased naltrexone effect estimates and standard errors. Results from study 2 largely replicated the findings of the nalmefene study conducted in Europe, whereby multiple imputation and pattern mixture models provided the best estimates of effects. Conclusions: Assuming that missing=heavy drinking produces biased results of the treatment effect and should not be used to evaluate treatment effects in alcohol clinical trials. Multiple imputation, maximum likelihood, and pattern mixture models produce better estimates of treatment effect sizes and should be considered when analyzing alcohol clinical outcome trial data.

Learning Objectives:

- To learn new approaches for handling missing data in alcohol clinical trials.
- The consequences of assuming that missing = heavy drinking in alcohol clinical trials.

Literature References:

- Little RA, D'Agostino R, CohenML, Dickersin K, Emerson SS, Farrar JT, Frangakis C, Hogan JW, Molenberghs G, Murphy SA, Neaton JD, Rotnitzky A, Scharfstein D, Shih WJ, Siegel JP, Stern H (2012) The Prevention and Treatment of Missing Data in Clinical Trials. N Engl J Med 367:1355–1360.
- Hallgren, KA, Witkiewitz, K (in press). Missing Data in Alcohol Clinical Trials: A Comparison of Methods. Alcohol Clin Exper Res. doi: 10.1111/acer.12205

PANEL
10:45 AM – 12:15 PM

PANEL OVERVIEW:
NOVEL TREATMENTS IN BIPOLAR DISORDER: PRIMARY AND SECONDARY TARGETS

Katherine Burdick, Joseph R. Calabrese[1], Andrei Pikalov[2], Joseph F. Goldberg[3], Terence Ketter[4]
[1]Case Western Reserve School of Medicine, [2]Sunovion Pharmaceuticals Inc., [3]Icahn School of Medicine at Mount Sinai, [4]Stanford University School of Medicine

The past several decades have seen considerable progress in the treatment of bipolar disorder. After a relative dearth of rigorously controlled studies during the 20 years following the approval of lithium in 1970, large multicenter controlled studies targeting mania re-emerged in 1994. In the following decade, attention was focused on the proportion of time depressed, as well as related morbidity and mortality. Since 2003, randomized controlled trials have supported the efficacy of several pharmacological agents for bipolar depression (i.e., olanzapine-fluoxetine combination, quetiapine, and lurasidone). Although additional studies are needed to expand options for treating affective symptoms in bipolar patients, an emerging and increasingly persuasive database now suggests that the field should extend its attention to other critical domains, such as the cognitive deficits associated with the illness. The proposed symposium will provide methodological recommendations and highlight the importance of considering primary and secondary targets and the complex interactions among them. Dr. Joseph Calabrese (Case Western) will present data from two pivotal bipolar depression trials of novel cognition-relevant agents, lurasidone and armodafinil. This will provide an example of a positive and a negative trial for primary outcome measures targeting the affective symptoms in bipolar disorder that will serve as a platform for discussing secondary targets. Dr. Andrei Pikalov (Sunovion) will present the preclinical evidence supporting lurasidone's efficacy in treating cognitive impairment. He will also describe results from secondary analyses focused on neurocognitive function in the lurasidone schizophrenia studies. Dr. Katherine Burdick (Mount Sinai) will then discuss the challenges inherent to cognitive trial design in bipolar patients and make recommendations for future studies. This will be done using both lurasidone and armodafinil as examples of agents with promising potential for cognitive efficacy. Finally, Dr. Joseph Goldberg (Mount Sinai) will describe several ways in which the interplay between affective symptoms and cognition can be controlled for in study design. In addition, he will highlight statistical approaches that might allow for a better understanding of the potential interactions between mood state and cognitive outcome. Dr. Terrance Ketter (Stanford University) will serve as the discussant who will tie these talks together and guide audience participation.

Learning Objectives:

- To learn about recent clinical trial outcomes in bipolar depression as they might relate to targeting secondary outcome such as cognition.
- To identify challenges associated with conducting clinical trials of cognition in bipolar illness.

INDIVIDUAL ABSTRACT:
METHODOLOGICAL CONSIDERATIONS IN THE DESIGN AND CONDUCT OF ACUTE ADJUNCTIVE BIPOLAR DEPRESSION TREATMENT TRIALS

Joseph R. Calabrese
Case Western Reserve School of Medicine

Methodological Considerations in the Design and Conduct of Acute Adjunctive Bipolar Depression Treatment Trials Joseph R. Calabrese, MDKEYWORDS: bipolar depression; atypical antipsychotics; antidepressants. Up until recently, no pharmacotherapy had been approved for the short-term adjunctive treatment of bipolar depression. Monotherapy designs have generated good internal validity, but appear to artificially inflate therapeutic effect size. Two recent trials have employed adjunctive designs, which more closely parallel clinical practice. Lurasidone is an antipsychotic agent whose efficacy is mediated by a combination of D2 and 5HT2A antagonism; efficacy in depression is believed to be mediated by 5-HT7 antagonism. 179 received lurasidone 20-120mg plus either lithium or valproate and 161

adjunctive placebo over 6 weeks. On the primary, which was the MADRS, lurasidone was superior to placebo (P<0.05)(effect size=0.30). Item analyses resulted in significant improvement on the core symptoms of depression. Responders on lurasidone vs. placebo was 57% vs. 42%; p<0.01. Adverse event discontinuations were 6% on placebo and 7.9% for lurasidone. Number needed to treat to have a response was 7 and to harm was 100. Armodafinil is a weak dopamine reuptake inhibitor and evaluated using a more inclusive design allowing lithium, valproate, lamotrigine, aripiprazole, olanzapine, ziprasidone, or risperidone, which would be expected to deflate effect size. 199 received armodafinil 150mg and 201 adjunctive placebo over 8 weeks. On the primary, which was the IDS-C30, armodafinil 150mg was superior to placebo (P<0.009) (effect size=0.28). Item analyses revealed a significant and novel spectrum of efficacy, including resulted in significant improvement for panic/phobic symptoms, increased appetite, concentration/decisions, energy/fatigability, and leaden paralysis/physical energy. This spectrum of efficacy appears to be complementary to the traditional spectrum of efficacy observed in acute bipolar depressions trials. Responders on armodafinil vs. placebo was 46% vs. 34%; p=0.015. Adverse events discontinuations were 4% on placebo and 6% for armodafinil. Number needed to treat to have a response was 9 and to harm was 100. Adjunctive study designs appear to be accompanied by more realistic therapeutic effects sizes and improved generalizability. Both monotherapy and adjunctive study designs should be concurrently conducted and prioritized in the future. The smaller effect sizes observed during the conduct of adjunctive trial designs should not be viewed as reflecting lack of efficacy. Rather, these designs should be viewed as reflecting comparable efficacy with improved external validity and should be prioritized in the future.

Learning Objectives:

- Attendees will become familiarized with design features relevant to the conducted of acute adjunctive bipolar depression treatment trials.
- Attendees will become familiar with the need to balance the need for assay sensitivity ('did the study work') with external validity (were the findings clinically relevant and generalizable to the community setting.

Literature References:

- Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, Calabrese J: Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. Am J Psychiatry. 2013 Oct 30 [Epub ahead of print].
- Calabrese J, Frye M, Yang R, Ketter T for the Armodafinil Treatment Trial Study NetworkEfficacy and Safety of Adjunctive Armodafinil in Adults With Major Depressive Episodes Associated With Bipolar I Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. J Clin Psychiatry. In Press.

INDIVIDUAL ABSTRACT:
EFFECT OF LURASIDONE ON COGNITIVE IMPAIRMENT: FROM THE LAB TO THE CLINIC

Andrei Pikalov
Sunovion Pharmaceuticals, Inc.

Lurasidone is an atypical antipsychotic that has been approved by the FDA for the treatment of schizophrenia and bipolar depression. The effects of lurasidone on aspects of cognitive function has been evaluated in a series of pre-clinical behavioral tests, including the passive-avoidance

and Morris water maze tests (assessing learning and memory), radial-arm maze test (working memory), the novel object recognition test (NOR), and the object retrieval with detour task (ORD; executive function and attention). In this pre-clinical battery, lurasidone restored MK-801-induced memory impairment in the passive avoidance and Morris water maze tests, and improved working memory in the radial-arm maze test. Treatment with lurasidone also improved sub-chronic PCP- induced deficits in novel object recognition in rats, and increased the success rate of monkeys in performing an object retrieval with detour task. In addition to its effects in behavioral models, chronic treatment with lurasidone has been found to upregulate brain-derived neurotrophic factor (BDNF) expression in rat prefrontal cortex, and to facilitate hippocampal BDNF transcription following acute stress. The potential effectiveness of lurasidone in treating cognitive deficits associated with schizophrenia has been evaluated in a recent trial in which patients with an acute exacerbation of schizophrenia were randomized to 6 weeks of double-blind, placebo-controlled treatment with lurasidone or quetiapine-XR. Upon completion of the initial 6-week study, eligible patients were enrolled in a 1-year, double-blind extension study, where patients continued treatment with either flexible-dose lurasidone 40-160 mg/d or quetiapine-XR 200-600 mg/d. Patients who had been treated initially with placebo were switched in blinded fashion to flexible dose treatment with lurasidone. The Cog State computerized cognitive battery was administered at pre-treatment baseline, week 6, and months 3 and 6 of the double-blind extension phase. For the evaluable sample with valid Cog State scores (N=267), lurasidone 160 mg was found to be significantly superior to both placebo and quetiapine XR on the neurocognitive composite score at month 6, while lurasidone 80 mg, quetiapine XR, and placebo did not differ. The University of California San Diego Performance-based Skills Assessment Brief (UPSA-B), which was concurrently administered, also showed superiority in cognitive performance for lurasidone compared with quetiapine-XR at both 3 and 6 months. CogState and UPSA-B scores were significantly correlated at baseline and for change over time. These findings, in a large, well-controlled patient population, provide preliminary clinical evidence that supports pre-clinical data indicating the potential of lurasidone for improving cognitive deficits in patients with psychotic illness. Assessment of the effect for lurasidone on cognition in bipolar illness needs further clinical confirmation.

Learning Objectives:

- To understand the effects of lurasidone in a battery of pre-clinical behavioral tests of cognitive function.
- To understand the potential clinical effects of lurasidone in treating cognitive deficits associated with schizophrenia.

Literature References:

- Horisawa T et al. The effects of selective antagonists of serotonin 5-HT7 and 5-HT1A receptors on MK-801-induced impairment of learning and memory in rats. Behav Brain Res 2011;220:83-90.
- Harvey PD et al. Effect of lurasidone on neurocognitive performance in patients with schizophrenia. Eur Neuropsychopharm 2013;23:1373-82.

INDIVIDUAL ABSTRACT:
METHODOLOGICAL CHALLENGES TO COGNITIVE TRIALS IN BIPOLAR DISORDER

Katherine Burdick

Mount Sinai School of Medicine
Objective: Neurocognitive impairment in patients with schizophrenia has been recognized for more than a century. In contrast, only very recently have significant neurocognitive deficits been recognized in bipolar disorder. Converging data suggest the importance of cognitive problems in relation to quality of life in bipolar disorder, highlighting the need for treatment and prevention efforts targeting cognition in bipolar patients. Method: A literature review was undertaken to identify illness-specific challenges relevant to the design and conduct of treatment trials targeting neurocognition in bipolar disorder. Results: Neurocognitive deficits in attention, verbal learning, and executive function are core features of bipolar disorder that commonly result in marked impairment of everyday functioning. Future treatment trials targeting cognitive deficits will be met with methodological challenges due to the inherent complexity and heterogeneity of the disorder, including significant diagnostic comorbidities, the episodic nature of the illness, frequent use of polypharmacy, cognitive heterogeneity, and a lack of consensus regarding measurement of cognition and outcome in bipolar patients. Trial design recommendations comprise exclusion of certain syndromal level comorbid diagnoses and current affective instability, restrictions on numbers and types of medications, and use of pre-screening assessment to ensure enrollment of subjects with adequate objective evidence of baseline cognitive impairment. Conclusions: Clinical trials to address cognitive deficits in bipolar disorder face distinctive design challenges. As such trials move from proof-of-concept to confirmation of clinical efficacy, it will be important to incorporate distinctive design modifications to adequately address these challenges and increase the likelihood of demonstrating cognitive remediation effects.

Learning Objectives:

- To identify challenges that are specific to clinical trial design in bipolar patients when considering cognitive enhancement opportunities.
- To make initial recommendations regarding best approaches to handle these challenges in a systematic manner.

Literature References:

- Burdick KE, Braga RJ, Nnadi CU, Shaya Y, Stearns WH, Malhotra AK. Placebo-controlled adjunctive trial of pramipexole in patients with bipolar disorder: targeting cognitive dysfunction. J Clin Psychiatry. 2012 Jan;73(1):103-12. doi: 10.4088/JCP.11m07299. Epub 2011 Nov 29. PubMed PMID: 22152405.
- Keefe RS, Buchanan RW, Marder SR, Schooler NR, Dugar A, Zivkov M, Stewart M. Clinical trials of potential cognitive-enhancing drugs in schizophrenia: what have we learned so far? Schizophr Bull. 2013 Mar;39(2):417-35. doi: 10.1093/schbul/sbr153. Epub 2011 Nov 22. Review. PubMed PMID: 22114098; PubMed Central PMCID: PMC3576170.

INDIVIDUAL ABSTRACT:
INTERACTION EFFECTS BETWEEN AFFECTIVE SYMPTOMS AND COGNITIVE FUNCTION IN BIPOLAR DISORDER CLINICAL TRIALS

Joseph F. Goldberg
Icahn School of Medicine at Mount Sinai

Cognitive dysfunction and affective symptoms each represent important primary outcomes in clinical trials for bipolar disorder, yet these phenomena are often inter-related. Perhaps because the impact of cognitive dysfunction in bipolar disorder has only recently become recognized, few

intervention studies to date have formally examined it alongside affective symptoms in order to assess potential interactions between these phenomena. Shortcomings of existing studies include relatively small sample sizes and incomplete data collection of both cognitive and affective symptoms, the frequent use of subjective rather than objective performance measures of cognitive dysfunction, and limited breadth of cognitive testing batteries. Studies also must account for possible iatrogenic adverse cognitive effects with pharmacotherapies used to improve depression, such as highly antihistaminergic atypical antipsychotics. This presentation will review several examples of pharmacologic intervention trials in bipolar disorder in which a focus on one domain either did or did not include significant secondary effects warranting further investigation. Pertinent methodologic issues for clinical trial designs involve whether changes in cognitive function may moderate changes in mood symptoms or vice-versa, whether comorbid anxiety symptoms or residual psychotic features may confound such relationships, and whether certain cognitive domains (e.g., attention versus memory versus executive dysfunction) or affective symptom clusters (e.g., vegetative features versus dysfunctional attitudes) may be particularly closely inter-related, in ways that global measures may fail to identify. Analyses of covariance, stepwise linear regression models, and path analyses all offer useful data analytic strategies for examining hypothesized inter-relationships among these variables. Strategies will be discussed for the design of future bipolar disorder clinical trials, including issues regarding adequacy of statistical power, that allow for the parsing of interactions between cognitive and affective variables.

Learning Objectives:

- To describe inter-relationships between affective and cognitive symptom domains as target symptoms when treating patients with bipolar disorder.
- To discuss methodologic strategies for examining associations between cognitive effects and affective symptom effects in intervention trials for bipolar disorder.

Literature References:

- Burdick KE, Braga RJ, Nnadi CU, et al. Placebo-controlled adjunctive trial of pramipexole in patients with bipolar disorder: targeting cognitive dysfunction. J Clin Psychiatry 2012; 73: 103-112.
- Kaye NS, Graham J, Roberts J, et al. Effect of open-label lamotrigine as monotherapy and adjunctive therapy on the self-assessed cognitive function scores of patients with bipolar I disorder. J Clin Psychopharmacology 2007; 27: 387-391

PANEL
10:45 AM – 12:15 PM

PANEL OVERVIEW:
WEIGHING IN ON RELATIVE RISKS OF FETAL EXPOSURE TO PSYCHOTROPICS AND PSYCHIATRIC DISORDERS

Lee S. Cohen[1], Marlene Freeman[1], Margaret Altemus[2], Sonia Hernandez-Diaz[3]
[1]Massachusetts General Hospital, [2]Weill Medical College, Cornell University, [3]Harvard School of Public Health

Data accumulated over the last decade suggest that pregnancy is not a time of emotional well-being with respect to psychiatric disorder. High rates of relapse of psychiatric disorder following discontinuation of antidepressants and mood stabilizers in pregnant women taking these

medications for treatment of mood and anxiety disorders have been demonstrated in several studies. Investigators across the globe have provided evidence in numerous publications which further delineate the risk of major congenital malformations following fetal exposure to commonly used psychiatric medications such as SSRI's and certain mood stabilizers. Reproductive safety data for other agents such as second generation antipsychotics, which are widely used by women during childbearing years, are far more sparse. Concerns regarding the safest clinical approach to management of psychiatric disorder during pregnancy are appropriate, while growing attention has also demonstrated the adverse obstetrical and neonatal outcomes associated with untreated psychiatric disorder during pregnancy. The impact of untreated psychiatric disorder on maternal, fetal and neonatal well-being is a critical variable in the risk-benefit decision regarding the use of psychiatric medications during pregnancy. This scientific session will include three presentations that highlight available data which inform the decision regarding use of psychiatric medications during pregnancy. Dr. Lee S Cohen will present available data from the National Pregnancy Registry for Atypical Antipsychotics at Massachusetts General Hospital. This is a prospective investigation of reproductive safety of second generation antipsychotics. Data will be presented regarding risk for major congenital malformations among exposed cases and controls for the sample accessioned to date. Dr. Sonia Hernandez-Diaz will provide a critical overview of state-of-the science with respect to the ever growing number of reports which have described the risk for major congenital malformations associated with fetal exposure to selective serotonergic reuptake inhibitors (SSRI's). She will provide a roadmap for the clinician for understanding the variability across reports which have described varying amounts of risk associated with use of this class of medication during pregnancy. Dr. Margaret Altemus will speak to the other side of the risk-benefit decision regarding use of psychiatric medications during pregnancy as she reviews the available data regarding the impact of psychiatric disorder on maternal, fetal and neonatal well-being. Dr. Marlene Freeman will serve as Discussant for this session as she attempts to integrate the lessons which derive from each of these presentations as they inform clinicians and patients about the safest way to approach the potential use of psychiatric medications during pregnancy.

Learning Objectives:

- To critically review available reproductive safety data across atypical antipsycotics and SSRIs.
- To highlight the impact of untreated psychiatric disorder on maternal, obstetrical, and neonatal outcomes.

INDIVIDUAL ABSTRACT:
THE NATIONAL PREGNANCY REGISTRY FOR ATYPICAL ANTIPSYCHOTICS: EFFECTS OF FETAL EXPOSURE ON RISK FOR CONGENITAL MALFORMATIONS AND MATERNAL AND NEWBORN OUTCOMES

Lee S. Cohen
Massachusetts General Hospital

Atypical antipsychotics are widely used by reproductive-age women to treat a spectrum of psychiatric illnesses though reproductive safety data across these medicines are sparse. The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) at Massachusetts General Hospital was established to address this knowledge gap (www.womensmentalhealth.org/pregnancyregistry). Potentially eligible enrollees between the ages of 18-45 call a toll-free number (1-866-961-2388), or complete an online interest form located on the Registry's website. Women who have been exposed to an atypical antipsychotic

during pregnancy are considered cases; controls are those women who have not been exposed to these agents or any other known teratogen since becoming pregnant. Verbal consent from cases and controls is obtained for three phone interviews: (1) baseline, proximate to the time of enrollment, (2) 7 months gestation, and (3) 2-3 months postpartum. Medical records are obtained to abstract data regarding obstetrical, labor and delivery, and newborn outcomes. A trained research assistant blinded to medication exposure reviews the records to abstract relevant information regarding primary and secondary outcomes including: 1) rates of major malformations in infants, and 2) birth weight, gestational age at delivery, miscarriage rates, method of delivery, and delivery complications. Data on maternal health outcomes including weight gain across pregnancy and gestational hypertension/diabetes are also obtained. Potential major malformations are identified and relevant records are sent to a blinded dysmorphologist for adjudication. A Scientific Advisory Board reviews interim findings and determines release criteria for Registry findings. As of November 2013, total enrollment in the Registry was 378 (232 prospective exposures and 86 prospective controls). Subject retention for cases and controls has been high, as has rates of medical record procurement. This presentation will describe the structure of the NPRAA in detail as well as preliminary findings of risk estimates for major congenital malformations following fetal exposure to second generation antipsychotics.

Learning Objectives:

- To develop an understanding of available reproductive safety data on atypical antipsychotics.
- To provide a conceptual framework for assessing the risk-benefit of atypical antipsychotic use during pregnancy.

Literature References:

- McKenna K, Koren G, Tetelbaum M, et al. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J Clin Psychiatry. 2005;66:444-449.
- Habermann F, Fritzsche J, Fuhlbruck F, Wacker E, Allignol A, Weber-Schoendorfer C, et al. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. J Clin Psychopharmacol. 2013;33:453-62.

INDIVIDUAL ABSTRACT:
PRENATAL EXPOSURE TO SSRIS: SORTING THE EVER-GROWING DATA

Sonia Hernandez-Diaz
Harvard School of Public Health

With Thalidomide we learned that drugs can be potent teratogens and increase orders of magnitude the risk of specific malformations in fetuses exposed early in pregnancy. Afterward, scientific controversy led to the discontinuation of one of the best studied, and most likely safe, drugs in pregnant women: Bendectin. Since then, the evaluation of drug teratogenicity in humans has been marked by a fear to both under and over-reaction to findings. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy. SSRI use late in pregnancy has been associated with several adverse perinatal outcomes including prematurity and neonatal withdrawal. Initial studies on the use of SSRIs early in pregnancy had reported no meaningful association with congenital malformations. However, in 2005, the US Food and Drug Administration (FDA) warned healthcare professionals that early prenatal exposure to paroxetine may increase the risk of congenital cardiac malformations. Since then, there has been an exponential increase in the number of studies published on this topic; followed by a larger number of reviews and opinion pieces. Some studies found significant

associations between antidepressants and major congenital malformations and others did not. Based on the same original findings, some experts conclude evidence of harm and others evidence of safety. The issue of whether paroxetine in particular, or SSRIs in general, does in fact increase the risk for cardiovascular malformations remains unresolved. It is unclear whether the reported associations are causal (attributable to teratogenic effects of specific drugs), or due to systematic error (e.g., confounding by underlying depression) or chance in the context of multiple comparisons. On the other hand, the reported lack-of-association may be due to misclassification of exposure (e.g., non-compliance with prescriptions) or outcome (e.g., inaccurate diagnoses), or to inadequate statistical power. In this session, we will conduct an autopsy on the discrepant findings on SSRIs teartogenicity and discuss the final diagnosis: Thalidomide or Bendectin.

Learning Objectives:

- Critically review the accumulated evidence on the association between use of specific SSRIs during the first trimester and the risk of major congenital malformations in the offspring.
- Recognize challenges in the assessment of absolute risks and benefits associated with continuation and discontinuation of antidepressants during pregnancy.

Literature References:

- Cole JA, Ephross SA, Cosmatos IS, Walker AM. Paroxetine in the first trimester and the prevalence of congenital malformations. Pharmacoepidemiology and drug safety 2007;16:1075-85.
- Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. The New England journal of medicine 2007;356:2675-83.

INDIVIDUAL ABSTRACT:
IMPACT OF MATERNAL PSYCHIATRIC ILLNESS ON FETAL, OBSTETRICAL AND NEONATAL WELL-BEING

Margaret Altemus
Weill Medical College, Cornell University

There is accumulating evidence of associations between untreated mental illness and adverse fetal and neonatal outcomes, including shortened gestation, increased rates of cesarean section, and neurobehavioral symptoms in childhood. A challenge in interpreting these data is determining the degree to which mental illness contributes to adverse outcomes independent of genetic factors and adverse behaviors associated with mental illness such as maternal obesity, smoking, insomnia, and physical inactivity, which are also known to contribute to adverse outcome. These distinctions are important for determining the relative benefit of treatment in women who do not have associated unhealthy behaviors. In addition, more work is needed to identify underlying medical conditions such as hypothyroidism and sleep apnea that can contribute to both depression and adverse birth outcomes. In these conditions, treatment of the underlying medical disorder, not just the depression, is needed to prevent adverse birth outcomes. Although treatment of mental illness during pregnancy clearly benefits the mother and the mother-infant relationship postpartum, more work is needed to determine when and how treatment of mental illness during pregnancy mitigates adverse effects on offspring.

Learning Objectives:

- Review the evidence for adverse effects of untreated mental illness on fetal health, birth outcome, and child development.
- Understand the mechanisms through which mental illness may be associated with adverse birth outcomes, including direct effects of mental illness on pregnancy and fetal development, and the impact of medical factors and health behaviors on both mental illness and birth outcome.

Literature References:

- Spicer J, Werner E, Zhao J, Choi CW, Lopez-Pintado S, Feng T, Altemus M, Gyamfi C, Monk C. Ambulatory Assessments of Psychological and Peripheral Stress–Markers Predict Birth Outcomes in Teen Pregnancy. J Psychosomatic Research, 75:305-13, 2013
- Occhiogrosso M, Omran S, Altemus M Persistent Pulmonary Hypertension of the Newborn: Clinical and Translational Studies. Am J Psychiatry, 169:134-140, 2012

PHARMACEUTICAL PIPELINE PRESENTATIONS
2:00 PM – 4:00 PM

INDIVIDUAL ABSTRACT:
RESULTS OF A PHASE 2B CLINICAL TRIAL OF TC-5619, A SELECTIVE ALPHA 7 NEURONAL NICOTINIC RECEPTOR (NNR) AGONIST IN THE ADJUNCTIVE TREATMENT OF NEGATIVE SYMPTOMS AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

David Hosford, Chris Dvergsten, Jessica Beaver, Anthony Segreti, Steven Toler, Gaston Farr, Melissa Joseph, John Jett, Patrick Lippiello, Merouane Bencherif
Targacept, Inc.

Background: There are no approved medicines to treat negative symptoms or cognitive dysfunction in people with schizophrenia. These are common features of the condition that often prevent those whose positive symptoms are well-controlled from resuming or achieving their premorbid potential. TC-5619, a selective alpha 7 NNR agonist, showed statistically significant benefit in preclinical models of cognition and negative symptoms; and also showed statistically significant benefit in cognitive and negative symptoms in an early phase 2 adjunctive clinical trial in schizophrenia that was conducted in the US and India. Methods This phase 2B clinical trial was a double-blind, randomized, parallel group, fixed dose, placebo-controlled trial comparing TC-5619 vs. placebo in the adjunctive treatment of negative symptoms or cognitive dysfunction in well-controlled outpatients with schizophrenia. Sixty-six sites in the US, Russia, Ukraine, Hungry, Romania and Serbia randomized 477 patients into a 24-week treatment period in which they received either TC-5619 (5 mg or 50 mg po qd) or placebo in a 1:1:2 ratio. All atypical antipsychotics were permitted except clozapine. The primary endpoint, negative symptoms, was measured using the Scale to Assess Negative Symptoms (SANS), and the key secondary endpoints, cognition and functional ability, were measured using the Cogstate Schizophrenia Test Battery (CSTB) and the UCSD Performance-Based Skills Assessment-Brief version (UPSA-B). A variety of other endpoints included global clinical outcome, adverse events, vital signs, physical exam, laboratory and ECG measurements, movement disorders, suicidality, depression, and tobacco craving. Results: The majority of the randomized subjects were tobacco users and the demographic profile was consistent with other trials in this population. None of the primary, key secondary or secondary efficacy outcome measures showed a statistically significant benefit favoring either dose of TC-5619. Withdrawals of any kind

including those due to adverse events were low, and there were few serious adverse events. The previously established safety and tolerability profile was not altered by any unanticipated findings. Discussion: This well-conducted and robust phase 2B study did not confirm benefits of TC-5619 in negative or cognitive symptoms, but it did confirm that the compound was generally safe and well-tolerated. Reasons for the lack of benefit do not appear to include dose selection, site performance, or subpopulation factors.

INDIVIDUAL ABSTRACT:
AZD8529, A POSITIVE ALLOSTERIC MODULATOR OF THE MGLUR2 RECEPTOR FOR THE TREATMENT OF SCHIZOPHRENIA

Alan Cross
AstraZeneca Neuroscience Innovative Medicines Unit

Compelling evidence indicates that hypofunction of prefrontal cortex glutamate signaling may play an important role in schizophrenia. This is likely due to decreased activation of NMDA receptors located on GABAergic interneurons, resulting in a lack of downstream inhibition and disruption of cortical circuit activity. Activation of the mGluR2 receptor is proposed as a novel therapeutic strategy for schizophrenia, based on the hypothesis that this mechanism would counteract the glutamatergic disinhibition produced by NMDA receptor hypofunction. Activation of mGluR2 has been shown to reduce the working memory deficit induced by ketamine and one study showed an antipsychotic effect in acute schizophrenia, an effect not reproduced in subsequent studies. AZD8529 acts as a selective positive allosteric modulator of mGluR2, it potentiated the effects of glutamate at the recombinant human receptor with an EC50 of 193 nM and an Emax of 93% with little effect on other mGluR subtypes. In a rat hippocampal slice assay, AZD8529 enhanced DCG-IV-induced reduction in synaptic transmission at hippocampal Schaffer collateral synapses by 30%, with an EC50 of 87 nM. Administration of AZD8529 (10 umol/kg, s.c.) caused a modest (<10%), reduction in baseline firing of mPFC neurons in behaving rats. MK-801 (0.2 mg/kg, s.c.) led to an increase in firing rates of recorded neurons, accompanied by a profound disturbance in organization of cortical firing as measured by a large increase in the variability of firing rates. Administration of AZD8529 significantly reversed the MK-801-induced increase in firing rate variance reflecting a normalization of cortical function. AZD8529 was well tolerated in human volunteers, with CNS drug exposure confirmed through csf analysis. In human translational imaging studies, effects consistent with CNS mGluR2 activation were observed at clinically relevant plasma drug exposures. AZD8529 was examined in a proof of principle study in symptomatic patients with schizophrenia Following 7 days washout period, patients received AZD8529 40mg (n=58), risperidone 4mg (n=31), or placebo (n=55) for 28 days, clinical efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS). Whilst risperidone reduced PANSS total score change from baseline compared with placebo (D=-9.5, $p<0.001$), AZD8529 was without effect (D=1.3, $p=0.491$). The current data are not consistent with positive modulation of mGluR2 receptors as a mechanism for monotherapy to treat acute schizophrenia. It remains to be determined whether different treatment regimens and particularly adjunct treatment would provide benefit.

INDIVIDUAL ABSTRACT:
ADVANCING ITI-007: A NOVEL PRODUCT CANDIDATE FOR THE TREATMENT OF SCHIZOPHRENIA, BIPOLAR DISORDER AND OTHER NEUROPSYCHIATRIC INDICATIONS

Kimberly E. Vanover, Robert E. Davis, Sharon Mates

Intra-Cellular Therapies, Inc.

Background: ITI-007 is an investigational new drug that modulates serotonergic, dopaminergic, and glutamateric neurotransmission, with differing pharmacology depending on dose. ITI-007 is a potent serotonin 5-HT2A receptor antagonist with wide separation between 5-HT2A and other neuropharmacological targets. As the dose is increased, ITI-007 engages dopamine D2 receptors as a pre-synaptic partial agonist and post-synaptic antagonist with mesolimbic/mesocortical selectivity, indirectly enhances glutamatergic neurotransmission by increasing the phosphorylation of mesolimbic GluN2B subunits of N-methyl-D-aspartate (NMDA) channels, and inhibits serotonin reuptake. Together, these data suggest different therapeutic utility at low doses of ITI-007 compared to higher doses. Lower doses of ITI-007 have shown activity in improving sleep maintenance without disrupting cognition or next-day function. Lower doses are also being explored for the treatment of behavioral disturbances in dementia. Recently, higher doses were evaluated for the treatment of acute schizophrenia. Methods: ITI-007 was evaluated in a double-blind, placebo- and active-controlled study in patients with acute schizophrenia. Subjects (N=335) were randomized to receive 60 mg ITI-007, 120 mg ITI-007, 4 mg risperidone (active control) or placebo. The primary endpoint was change from baseline on the Positive and Negative Syndrome Scale (PANSS) total score after 28 days of treatment. Secondary endpoints included PANSS subscales and individual items as well as the Calgary Depression Scale for Schizophrenia (CDSS). Safety endpoints included assessment of motor function and clinical laboratory assessments of prolactin and metabolic parameters (e.g., insulin, glucose, cholesterol and triglycerides). Results: ITI-007 at 60 mg, but not 120 mg, demonstrated a statistically significant reduction in the change from baseline on total PANSS scores compared to placebo. Risperidone also significantly separated from placebo, demonstrating assay sensitivity. Unlike risperidone, ITI-007 (60 mg) did not increase motor side effects, prolactin levels or metabolic parameters. ITI-007 (60 mg) also demonstrated a response profile across the symptoms measured by PANSS consistent with improved social function and differentiated from risperidone's response profile. Discussion: ITI-007 represents a new approach to the treatment of a broad array of symptoms associated with schizophrenia. In the present study, ITI-007 was well tolerated in patients with acute schizophrenia. Consistent with its pharmacological profile, ITI-007 (60 mg) significantly improved symptoms consistent with improved social function. Lower doses are being assessed for safety and tolerability in healthy geriatric volunteers and patients with dementia. Phase 3 studies are being planned to evaluate ITI-007 for the treatment of schizophrenia and for the treatment of bipolar disorders.

INDIVIDUAL ABSTRACT:

A PILOT STUDY OF A NOVEL MONOAMINE TRIPLE REUPTAKE INHIBITOR EB-1020 SR IN THE TREATMENT OF ADHD IN ADULTS

Timothy Wilens[1], Andrew J. Cutler[2], Ann Childress[3], Randall D. Marshall[4], Mark Bradshaw[5], Frank Bymaster[6], Anthony McKinney[7], Stephen W. Hurt[8], Catherine O'Brien[7], Timothy Hsu[7]

[1]Massachusetts General Hospital, [2]Florida Clinical Research Center, LLC, [3]Psychiatry, [4]Alkermes, Inc., [5]GCP-MB, [6]Euthymics Bioscience Inc., [7]Neurovance, Inc., [8]Weill Cornell Medical College

Background: This pilot study was designed to evaluate EB 1020-SR as a novel non-stimulant treatment option for adult attention-deficit hyperactivity disorder (ADHD). EB1020-SR is a norepinephrine-preferring triple reuptake inhibitor with IC50 values for transporter reuptake inhibition of 6 nM, 38 nM, and 83 nM , for norepinephrine, dopamine and serotonin respectively. Methods: A total of 41 adult males with well-characterized ADHD enrolled in this 4-week,

single-blind study with 1-week placebo run-in. EB1020-SR was given twice daily and titrated to a target dose of 500 mg daily over 7 days. Outcomes assessed included ADHD, executive functioning, and tolerability. Results: 37 subjects completed the trial. EB 1020-SR produced a 21-point reduction on the ADHD Rating Scale-IV (endpoint mean score =17, $p<0.0001$) including significant reductions in inattentive ($p<0.0001$) and hyperactive impulsive symptoms ($p < 0.0001$). Overall, 68% of subjects were considered responders using the Clinical Global Impression of Improvement (much/very much improved). Clinically and statistically significant improvements in overall and specific domains of executive function using the Behavioral Inventory of Executive Functioning were also found (overall $p<0.0001$). No clinically meaningful trends in adverse events, laboratory values, vital signs, or ECG parameters were noted. Conclusions: EB 1020-SR appears effective in treating ADHD and executive functioning deficits in adult males. The maximum dose studied appears to be well tolerated. Based on these results, randomized, controlled studies of EB 1020 appear warranted.

INDIVIDUAL ABSTRACT:
METADOXINE EXTENDED RELEASE (MDX): A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF ADHD & OTHER COGNITIVE DISORDERS

Jonathan Rubin[1], *Yaron Daniely*[1], *Lenard Adler*[2]
[1]*Alcobra Pharma*, [2]*NYU School of Medicine*

Psychostimulants compromise the majority of the therapeutic landscape for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). However, some individuals may not respond or tolerate stimulants, some domains are less responsive to stimulants, and stimulants raise concerns for potential substance misuse or diversion. Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is an ion-pair salt of pyridoxine (vitamin B6) and 2-pyrrolidone-5-carboxylate (PCA, also known as L-PGA). Pyridoxine is a precursor of coenzymes such as pyridoxal phosphate. Pyridoxal phosphate-dependent enzymes are vital in the biosynthesis of the neurotransmitters serotonin, epinephrine, norepinephrine, and GABA. Metadoxine does not increase levels of brain neurotransmitters such as dopamine, norepinephrine and serotonin. In animal studies, Metadoxine has shown no signs of abuse or addiction potential. Metadoxine Extended Release (MDX) is a novel, immediate release and sustained release formulation in a bi-layer tablet. An open-label study of MDX in 40 adults with ADHD demonstrated efficacy on the Conners Adult ADHD Rating Scale (CAARS) and the Test of Variables of Attention (TOVA) and was generally well tolerated. We now report on two double-blind placebo controlled Phase 2 studies of MDX in adults with ADHD. A 6-week, randomized, double-blind, parallel comparison of 1400 mg MDX vs placebo in 120 adults with ADHD showed significant improvements in weekly-assessed CAARS Total ADHD Symptoms Score (-12.5 ±1.18SE versus -8.93 ±1.24, $P<0.02$) and TOVA ADHD score (5.07 ±1.19 versus 3.01 ±0.86, $P<0.02$). Improvements were statistically significant compared with placebo after 2 weeks. A sub-analysis of subjects with ADHD inattentive type (n=48) showed an even greater improvement in CAARS scores for subjects receiving MDX compared with placebo (-13.4 ±1.9 versus -6.3 ±1.4, $P<0.05$). Another randomized, double-blind, placebo-controlled, trial was conducted using a crossover design. This single-center study in 36 adult subjects with ADHD-PI evaluated MDX 700 mg, MDX 1400 mg, and placebo, each administered 1 week apart. TOVA assessments were performed 3 to 5 hours post-dose. The primary outcome was change from baseline in the TOVA ADHD score, which was statistically significant from baseline for MDX 1,400 mg compared with placebo (mean change 2.0, SD 4.2, P=.009). There were no serious adverse events or any meaningful differences in adverse events profile between the drug and placebo groups. MDX may provide an

important new treatment option for ADHD and other cognitive disorders with a rapid onset of effect and demonstrated efficacy in adult subjects with ADHD, particularly in patients with predominantly inattentive type ADHD, and an enhanced safety and tolerability profile. Learning Objectives: • Participants will learn about a new drug candidate, Metadoxine Extended Release (MDX), as a novel treatment for ADHD with attributes that may contribute to an enhanced efficacy, tolerability, and safety profile. • Participants will learn about the pharmacological profile of Metadoxine Extended Release (MDX), a non-dopaminergic, non-noradrenergic agent.

INDIVIDUAL ABSTRACT:

A RAPIDLY ACTING INTRANASAL TREATMENT FOR THE SYMPTOMS OF GAD

Michael R. Liebowitz[1], Louis Monti[1], Rita Hanover[2], Bernard Grosser[3]

[1]Pherin Pharmaceuticals, Inc., [2]Westport Compass, [3]University of Utah School of Medicine

Background. Although generalized anxiety disorder (GAD) is a common and sometimes disabling condition, there is a need for additional treatments other than benzodiazepines that can be used on a prn basis to help with the severe anxiety and distress that many affected individuals experience. PH94B is a new investigational drug for the acute treatment of Social Anxiety Disorder. Chemically, PH94B is an odorless, neuroactive steroid compound with proven lack of affinity to steroidal hormone receptors. It is thought to act via nasal chemosensory receptors that broadcast chemosensory information to specific brain areas (cingulate gyrus, hypothalamus, limbic amygdala, anterior gyrus and prefrontal cortex) which are different from the brain areas activated by olfactory stimuli. Earlier studies demonstrated that picomol quantities of PH94B induced dose-dependent membrane currents and increased Cai2+ in isolated human nasal chemosensory cells, and depolarization of the human nasal chemosensory epithelium, followed by small but significant decreases in heart rate, respiratory rate, electrodermal activity, and blinking reflex, and increased alpha-EEG and body temperature. A number of the volunteers spontaneously reported feeling distinctly calm and less nervous during these studies. Similar results were obtained in a Phase I dose escalation study. Methods. To continue this exploration of PH94B, 28 patients with GAD (DSM-IV) were enrolled in a randomized, placebo-controlled, double blind study. Following exclusion of placebo responders (n = 7) 21 patients were randomized to receive 200 pg PH94B or placebo in a one second aerosol pulse to the chemosensory epithelium of the anterior nasal septum. HAM-A, and clinical electrophysiological measures were administered at randomization (Baseline) and 30 and 60 min following treatment. Because of the small sample size and lack of power, effect sizes (Cohen's d) were evaluated in addition to between-group comparisons. Results. Nineteen completed the study (2 early terminators). Thirty minutes after treatment there was mean reduction of 32.0% (8.7 points) for the PH94B group (n = 11) and 19.6% (5.1 points)for the Placebo group (n = 8) in total HAM-A ($p = 0.09$, one-tail t-test; Cohen's $d = 0.644$) Electrophysiological changes (respiratory, cardiac, and electrodermal frequency), concordant with the reduction in anxiety, were significantly greater for the PH94B group (p's < 0.003, one-tail; Cohen's d range: 1.3 to 8.0). Further exploration of group differences for individual HAM-A item scores revealed impressive effect sizes for improvement in Anxious Mood Cognition Depressed Mood Cardiovascular Symptoms and Other Autonomic Symptoms Cohen's d range: from 0.469 to 1.59). After 60 min, all significant improvements and group differences had disappeared. Conclusions. PH94B may be useful as a prn treatment for GAD, although further trials with larger samples are indicated. PH94B may be useful in other anxiety states where rapid, temporary relief would be of benefit, like performance and social anxiety that is part of social anxiety disorder. In fact, this was

recently demonstrated in a placebo controlled trial. Nasal chemosensory cells may be a portal of entry for substances affecting feeling states.

INDIVIDUAL ABSTRACT:
LUPRON IN COMBINATION WITH AN ACETYLCHOLINESTERASE INHIBITOR HALTS COGNITIVE DECLINE IN WOMEN WITH ALZHEIMER'S DISEASE OVER A 48 WEEK PERIOD

Richard Bowen[1], *Craig Atwood*[2]
[1]*OTB Research,* [2]*University of Wisconsin, Madison*

Context: Evidence for suppressing gonadotropin-releasing hormone (GnRH) and gonadotropin signaling in the treatment of Alzheimer's disease (AD) comes from a growing number of epidemiological, preclinical and biological studies. Objective: To determine the efficacy and safety of suppressing GnRH and gonadotropin signaling with leuprolide acetate (Lupron Depot®) in the treatment of women with mild to moderate AD. Design: A 48 week, double-blind, placebo-controlled, dose-ranging study conducted in women aged 65 years or older with mild to moderate AD. Setting: Five study sites in the United States. Participants: A total of 109 women with mild to moderate AD and a Mini-Mental State Exam score between 12 and 24 inclusive. Interventions: Participants were randomized to low dose Lupron Depot® (11.25 mg leuprolide acetate), high dose Lupron Depot® (22.5 mg leuprolide acetate) or placebo injections per 12 weeks. Main Outcome Measures: The primary efficacy parameters were the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC). Secondary efficacy parameters were the Neuropsychiatric Inventory (NPI), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL), Burden Interview (BI), and ADCS-Severity Rating. Results: In the primary analysis there was a trend, although not statistically significant, in favor of the high dose Lupron group on the ADAS-Cog. The mean decline in the ADAS-Cog scores after 48 weeks of treatment in the placebo, low- and high-dose groups were 2.4, 4.9 and 1.7, respectively. A similar, although not as pronounced trend, was observed for ADCS-CGIC scores. The number of patients who exhibited a decline in CGIC scores in the placebo, low- and high-dose groups were 20 (54%), 26 (72%) and 18 (39%), respectively. There were no statistically significant differences in any of the secondary efficacy parameters. However, in the apriori designated subgroup analysis of patients taking an acetylcholine esterase inhibitor (AChEI) there was a statistically significant benefit as determined by ADAS-Cog, ADCS-CGIC and ADCS-ADL in the high dose group compared to both the low dose and placebo groups. The mean decline in ADAS-Cog after 48 weeks in the high-dose group was 0.18 compared to those taking low dose 4.21 and placebo 3.30. Similarly, on the ADCS-CGIC 38% percent of subjects experienced decline in the high-dose group compared to 82% in the low dose group and 63% in the placebo group. The mean decline in the ADCS-ADL in the high dose group was -0.54 compared to -8.00 and -6.85 in the low dose and placebo groups respectively. No differences between treatment groups were seen on the NPI, ADCS-CGI Severity Rating, or the BI in the subgroup analysis. Conclusions: Cognitive function was preserved in patients treated with high dose Lupron who were already using AChEI's. However, caution should be used in the interpretation of the results due to the fact that; the study size is small, baseline demographics were not compared for the subgroup, and the data was not adjusted for multiple analyses. The positive interaction between Lupron and AChEI's warrants further investigation for the treatment of AD.

INDIVIDUAL ABSTRACT:
EFFICACY AND SAFETY OF A NOVEL MGLU2 RECEPTOR POSITIVE ALLOSTERIC MODULATOR AS AN ADJUNCTIVE TREATMENT TO AN SSRI/SNRI IN THE TREATMENT OF ANXIOUS DEPRESSION

Justine Kent[1], Ella Daly[1], Ceusters Marc[2], Iva Kezic[2], Rosanne Lane[2], Lim Pilar[2], De Smedt Heidi[2], Mazzucco Christine[2], Peter DeBoer[2], Luc Van Nueten[2], Wayne Drevets[2]
[1]Janssen, [2]Janseen R&D

This presentation will discuss the recent results of a Phase 2a proof-of-concept study of a novel mGluR2 positive allosteric modulator (PAM) in the adjunctive treatment of Major Depressive Disorder (MDD) with significant anxious features. This was a multicenter, double-blind, placebo-controlled, flexibly-dosed study of an mGluR2 PAM in adult patients with MDD with significant anxious symptoms. The study consisted of 3 phases: a screening phase of up to 2 weeks, an 8-week double-blind treatment phase (including two 4-week treatment periods), and a 2-week post treatment follow-up phase. Methods: Entry requirements for patients included: DSM-IV diagnosis of MDD, Hamilton Depression Rating Scale-17 (HDRS-17) score of ≥ 18, HDRS Anxiety Somatization Factor score of ≥ 7 (to ensure adequate level of anxiety), and current treatment with an SSRI/SNRI at an adequate dose for a minimum of 4 weeks at screening, and a maximum of 12 weeks, with insufficient response. Comorbid Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and Panic Disorder (PD) were allowed. A doubly-randomized design was employed. At entry into Period 1, patients were randomly assigned in a 1:1 ratio to the mGluR2 PAM or Placebo as adjunctive treatment to their baseline antidepressant therapy. The mGluR2 PAM drug was flexibly dosed in the range of 50mg to 150mg b.i.d. At the end of Period 1, those patients exposed to Placebo who continued to meet severity criteria (HDRS-17 score ≥ 18 and HDRS Anxiety Somatization Factor score of ≥ 7) were re-randomized in a 1:1 ratio to mGluR2 PAM or Placebo. All other subjects underwent a sham re-randomization and continued on their same treatment. Results: Of 121 subjects randomized, 107 entered Period 2, during which 22 subjects treated with Placebo in Period 1, and meeting the criteria for nonresponse, were re-randomized. No efficacy signal was detected on the primary outcome measure, the 6-item Hamilton Anxiety Scale (HAM-A-6), based on the weighted combination test (p=0.51); however, efficacy signals were evident on several secondary outcome measures of both depression (HDRS-17 total score, 6-item subscale of HDRS-17 assessing core depressive symptoms (HAM-D-6), Inventory of Depressive Symptomatology (IDS-C30) and anxiety (HDRS Anxiety Somatization Factor, IDS-C30 Anxiety Subscale). The drug demonstrated a benign safety profile and was well-tolerated, with the most common treatment emergent adverse events being dizziness-related events. Conclusions: The totality of data do not suggest a strong drug effect for this mGluR2 PAM in the adjunctive treatment of anxious depression. Although glutamatergic mechanisms are felt to play a role in this disorder, administration of an mGluR2 PAM in the dose range tested did not appear to have a clinically significant impact on symptoms. Overall, the drug was safe and well-tolerated in the dosing range studied.

Learning Objectives:

- Participants will understand the rationale for treatment approaches aimed at modulating glutamatergic neurotransmission in the anxious depressed population.

- At the conclusion of this session, participants will be aware of the results of a proof-of-concept study with a novel mGluR2 PAM, and understand the impact of these results on further pursuit of this target in depression.

INDIVIDUAL ABSTRACT:
A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP, DOSE FREQUENCY STUDY OF INTRAVENOUS KETAMINE IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

Jaskaran Singh
Janssen Research and Development, LLC

Background: Ketamine has been shown to produce rapid antidepressant action in patients with treatment-resistant depression (TRD). The purpose of this phase 2 trial is to evaluate if twice weekly (2X/wk) dosing will be as efficacious as 3 times per week (3X/wk) in sustaining the antidepressant effects of ketamine. Methods: Patients with TRD were randomized 1:1:1:1 to receive one of 4 intravenous 4-week treatments: 2X/wk or 3X/wk placebo, or 2X/wk or 3X/wk ketamine (0.5mg/kg as an infusion over 40 minutes). The primary efficacy endpoint was the change from baseline to Day 15 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Safety and secondary efficacy endpoints were also assessed. Results: Sixty-seven (intent-to-treat) patients were enrolled. The mean age was 44 years and the average baseline MADRS total score was 35. The primary efficacy endpoint showed significant improvement in the MADRS total score for both ketamine dose frequency groups compared with corresponding placebo groups ($p < 0.001$ in both groups, 1-sided). The differences of least squares mean (SE) change from baseline between ketamine and placebo were -16.0 (3.74) for the 2X/wk group and -16.4 (2.40) for the 3X/wk group. During the double-blind treatment phase, the most common ($\geq$ 20% of patients) treatment-emergent adverse events were headache, anxiety, dissociation, nausea, and dizziness. There were 2 non drug-related serious adverse events (anxiety and suicide attempt) in the ketamine 2X/wk group. No death was reported. We will also review data for a second study (efficacy and safety). Conclusions: Ketamine dosed 2X/wk or 3X/wk demonstrated similar efficacy and significant changes in the MADRS total score from baseline to Day 15, and was generally well tolerated.

Learning Objectives:

- Attendees will learn about challenges of developing a new drug with a novel MOA.
- Attendees will learn about combination of drug-device development.

INDIVIDUAL ABSTRACT:
RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, PHASE 2/3 STUDY TO DETERMINE THE SHORT-TERM (6-WEEK) AND LONG-TERM (6 MONTH) COGNITIVE AND ANTI-PSYCHOTIC EFFICACY, SAFETY AND TOLERABILITY OF CYP-1020 COMPARED TO RISPERIDONE

Jonathan Rabinowitz
Bar Ilan University

Background: CYP-1020 (aka BL-1020) is a y-aminobutyric acid (GABA) enhanced antipsychotic that combines dopamine antagonism with GABA agonist activity. A previous study found possible pro-cognitive effects of CYP-1020 (20-30 mg) as compared to placebo and risperidone (2-8mg/d) in chronic schizophrenia. The objective of the current study was to test the

hypothesis that CYP-1020 would have pro-cognitive benefits as compared to risperidone after 6 weeks of treatment in patients experiencing acute exacerbations of schizophrenia. Secondary objectives included evaluating pro-cognitive benefits after 12 and 24 weeks and to compare antipsychotic efficacy of the treatments after 6, 12 and 24 weeks. Methods: Two hundred and sixty nine patients, out of 450 planned, aged 18 to 50 meeting criteria for DSM-IV-TR diagnosis of chronic schizophrenia were randomized double-blind to receive CYP-1020 (15-35 mg per day), or risperidone (2-6 mg/day) and treated for up to 24 weeks. The primary efficacy measure, MCCB (MATRICS Consensus Cognition Battery) and secondary measures, UPSA-B (University of California Performance-Based Skills Assessment-Brief Version) and PSP (Personal and Social Performance scale), were administered at baseline and week 6, 12 and 24 or end point. The PANSS and CGI-S were administered at all study weeks except for week 1. Readiness for discharge was rated at weeks 2, 4, 6 and 8. Patients underwent weekly assessments of vital signs, safety which included the SAS (Simpson Angus Scale), AIMS (Abnormal Involuntary Movement Scale), BAS (Barnes Akathisia Scale) and inventory of concomitant medications. Results: The study was terminated after the interim analysis suggested that the study would not reach its primary endpoint. There was no statistically significant difference on cognitive benefits on the MCCB total composite score. However, on the Mayer-Salovey-Caruso Emotional Intelligence Test, which was used to measure social cognition, and included in the MCCB total score, differences were found favoring CYP-1020. This difference was noticeable starting at week 12, and reached significance (p=.051) at week 24 endpoint. On the PANSS there was a significant treatment by country interaction with CYP-1020 group showing significantly greater reduction on the PANSS total score than Risperidone group in Romania at weeks 6, 12 and 24. There were no significant or treatment group differences on the CGI, PSP, UPSA or RDQ. There were no notable differences on vital signs, TAE's, SAE's, SAS, BAS and AIMS. Increase in prolactin was substantially lower in CYP-1020 as compared to risperidone. Discussion: The current study does not support a superiority of CYP-1020 over risperidone on general cognition. However, results suggest a superiority on social cognition. It should be noted that social cognition is not highly correlated with general cognition. There is an emerging literature that examines the role of antipsychotics in improving social cognition. This could be a future area to explore for CYP-1020.

PANEL
4:15 PM – 5:45 PM

PANEL OVERVIEW:
BIPOLAR CHOICE (CLINICAL HEALTH OUTCOMES INITIATIVE IN COMPARATIVE EFFECTIVENESS):A PRAGMATIC TRIAL OF LITHIUM VS. A SECOND GENERATION ANTIPSYCHOTIC FOR BIPOLAR DISORDER

Terence Ketter[1], Andrew Nierenberg[2], Edward S. Friedman[3], David Kemp[4], Mauricio Tohen[5]
[1]Stanford University School of Medicine, [2]Massachusetts General Hospital, [3]University of Pittsburgh School of Medicine, [4]Case Western Reserve University, [5]U of New Mexico, Department of Psychiatry

Background: Bipolar disorder is one of the 10 most disabling medical conditions worldwide. While lithium (Li) has been used extensively for bipolar disorder since the 1950s, second generation antipsychotics (SGAs) have supplanted Li since the beginning of the century. To date, however, no randomized comparative effectiveness study has compared Li and any SGA. Methods: Participants with bipolar I or II disorder were randomized to receive Li (n=240) or the

SGA quetiapine (QTP; n=242) for 6 months at 11 sites in the United States. Li and QTP were combined with other medications for bipolar disorder consistent with contemporary clinical practice (adjunctive personalized treatment – APT, excluding QTP or any other SGA for Li-treated patients and excluding Li or any other SGA for QTP-treated patients). Co-primary outcome measures were the Clinical Global Impression-Efficacy Index (CGI-EI) and Necessary Clinical Adjustments (NCAs) which measured changes in APT medications. Other measures included the Bipolar Inventory of Symptoms Scale (BISS), Framingham Cardiovascular Risk Score, functioning, quality of life, suicidal ideation and behavior, and adverse effects. Results: Differences between groups in changes in CGI-EI and NCAs were not statistically significant. Changes in CGI-EI with QTP+APT were better than Li+APT for participants with greater manic or hypomanic symptoms. We found no other significant group differences on secondary measures. Conclusions: Despite adequate power to detect clinically meaningful effects, we found no significant differences between Li+APT and QTP+APT across 6months of treatment on most measures.

Learning Objectives:

- To appreciate the comparative effectiveness of lithium versus quetiapine plus adjunctive personalized treatment over six months in bipolar disorder patients in the Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) study.
- To understand the strengths and limitations of the clinical trials methodology employed in the Bipolar CHOICE study.

INDIVIDUAL ABSTRACT:
BIPOLAR CHOICE (CLINICAL HEALTH OUTCOMES INITIATIVE IN COMPARATIVE EFFECTIVENESS): RATIONALE, DESIGN, AND DEMOGRAPHICS

Edward S. Friedman
University of Pittsburgh School of Medicine

Bipolar disorder is a severe, recurrent, and lifelong illness affecting 4.5% of the U.S. population, and is one of the top 10 most disabling medical conditions worldwide. While lithium (Li) has been used extensively for bipolar disorder, second generation antipsychotics (SGAs) have rapidly supplanted Li since 1998. To date, however, no randomized comparative effectiveness studies have compared Li and any SGA. Participants with Bipolar I or II disorder were randomized to receive Li (n=240) or the SGA quetiapine (QTP; n=242) for 6 months across 11 sites. Li and QTP were combined with other medications for bipolar disorder consistent with typical clinical practice (adjunctive personalized treatment - APT, excluding QTP or any other SGA for Li treated patients and excluding Li or any other SGA for QTP patients). We assessed benefits and harms with the Clinical Global Impression-Efficacy Index (CGI-EI) and Necessary Clinical Adjustments (NCAs) that measured changes in APT medications. We also assessed symptoms with the Bipolar Inventory of Symptoms Scale (BISS), Framingham Cardiovascular Risk Score, functioning, quality of life, suicidal ideation and behavior, and adverse effects. To maximize generalizability CHOICE-BP used broad inclusion and narrow inclusion criteria to improve assay sensitivity and internal validity. This talk will present the design and rationale of the study, and review the demographic characteristics of the study cohort.

Learning Objectives:

- To understand the rationale and design of the CHOICE-BP study.
- To understand the demographic characteristics of the CHOICE-BP study population.

Literature References:

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INDIVIDUAL ABSTRACT:
BIPOLAR CHOICE (CLINICAL HEALTH OUTCOMES INITIATIVE IN COMPARATIVE EFFECTIVENESS)

Andrew Nierenberg
Massachusetts General Hospital

Background: Bipolar disorder (BP) is among the 10 most disabling medical conditions worldwide. While lithium (Li) has been used extensively for BP since the 1970s, second generation antipsychotics (SGAs) have supplanted Li since 1998. To date, no randomized comparative effectiveness studies have compared Li and any SGA. Methods: Participants with BP I or II were randomized for 6 months to receive Li (n=240) or quetiapine (QTP; n=242). Li and QTP were combined with other medications for BP consistent with typical clinical practice (adjunctive personalized treatment - APT, excluding any SGA for the Li+APT group and excluding Li or any other SGA for the QTP+ATP group). Co-primary outcome measures included Clinical Global Impression-Efficacy Index (CGI-EI) and Necessary Clinical Adjustments (NCAs) which measured changes in APT. Secondary measures included a full range of symptoms, cardiovascular risk, functioning, quality of life, suicidal ideation and behavior, and adverse events. Results: Participants improved across all measures and over 20% had a sustained response. Primary (CGI-EI; p=0.59, NCA; p=0.15), and secondary outcome changes were statistically similar. For participants with greater manic/hypomanic symptoms, CGI-EI changes were significantly more favorable with QTP+APT (p=0.02). Among those with anxiety, the Li+APT group had fewer NCAs per month (p=0.02).Conclusions: Despite adequate power to detect clinically meaningful differences, we found mostly similar benefits with Li+APT and QTP+APT across 6 months of treatment for BP. Our findings contrast with heuristics about choosing Li or QTP based on depression, anxiety, or suicidal risk.

Learning Objectives:

- Comparative Effectiveness Research Design
- Outcomes of the CHOICE Study

Literature References:

- Pillarella J, Higashi A, Alexander GC, Conti R. Trends in use of second-generation antipsychotics for treatment of bipolar disorder in the United States, 1998-2009. Psychiatric Services. 2012;63(1):83-6.
- Nierenberg AA, Sylvia L G, Leon, A C, Reilly-Harrington, N A, Shesler, L W, McElroy, S L, Friedman, E S, Thase, M E, Shelton, R C, Bowden, C, Tohen, M, Singh, V, Deckersbach, T,

Ketter, T, Kocsis, J, McInnis, M G, Schoenfeld, D, Bobo, W V, Calabrese, J R, Bipolar CHOICE Study Group. Clinical Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE): A Pragmatic Trial of Complex Treatment for a Complex Disorder. Clinical Trials. In Press.

INDIVIDUAL ABSTRACT:
BIPOLAR CHOICE SAFETY AND TOLERABILITY OUTCOMES: FOCUS ON OBESITY AND CARDIOMETABOLIC HEALTH

David Kemp
Case Western Reserve University

Several studies have shown that adults and adolescents with bipolar disorder have an increased risk of overweight, obesity, and metabolic syndrome. Given the bi-directional relationship between obesity and depression, some studies have also found treatment outcomes to be moderated by cardiometabolic risk factors. Thus, the safety and tolerability outcomes of the Bipolar CHOICE trial were analyzed, with an emphasis on cardiometabolic outcomes. Both the lithium (Li) plus adjunctive personalized treatment (APT) and quetiapine (QTP) + APT groups experienced a similar improvement in mood symptoms as measured by the Clinical Global Impression Efficacy Index (CGI-EI). However, QTP+APT resulted in modestly greater adverse effects over the 6 months of treatment on the Frequency, Intensity, and Side Effects Rating scale (FISER) on the measures of frequency (p=.05), intensity (p=.01), and impairment (p=.01) compared to Li+APT, with most of the differences occurring within the first 3 months. Both groups had similar rates of premature discontinuation. Consistent with other studies that have found comorbid medical conditions to be highly prevalent and associated with course of illness and symptom burden, over 96% of participants in CHOICE met criteria for at least one comorbid medical condition. Specifically, longer durations of depression were associated with a higher likelihood of having a cardiometabolic condition. Metabolic syndrome was present in 29% (138/469) of the sample and 44% (212/479) were obese (BMI >= 30). Stage II (BMI >= 35 to <40) and Stage III (BMI >= 40) obesity were met by 12% (57/479) and 9% (42/479) of participants, respectively. A multivariate logistic regression model to predict general obesity identified that increasing age, female gender, being married, and the presence of a current anxiety disorder were associated with increased odds of obesity, whereas being employed and having a higher overall CGI score were associated with a lower odds of obesity. Relating obesity status to treatment outcome, obese participants were less likely to show improvement over 6 months on the CGI overall score (p<.01), Bipolar Inventory of Symptoms Scale (BISS) total score (p=.02), and BISS depression score (p<.01). Moreover, obese participants experienced lower improvement in quality of life and functioning as measured by change in the total score on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (p=.04) and Range of Impaired Functioning Tool (LIFE-RIFT) (p<.01) , respectively. In summary, both Li+APT and QTP+APT were similarly effective and similarly well tolerated. Obesity status was related to both clinical presentation and treatment outcome.

Learning Objectives:
- Identify the general medical and cardiometabolic burden experienced by participants in the Bipolar CHOICE comparative effectiveness trial.
- Recognize the effect of obesity on treatment outcomes including change in symptom severity and quality of life.

Literature References:

- Nierenberg AA, et al. 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. In press.
- Kemp DE, et al. General medical burden in bipolar disorder: findings from the LiTMUS comparative effectiveness trial. Acta Psychiatr Scand. 2014 Jan;129(1):24-34.

PANEL
4:15 PM – 5:45 PM

PANEL OVERVIEW:
NIAAA PANEL SESSION: ADVANCES IN TREATMENTS FOR PTSD AND ALCOHOL COMORBIDITY

Raye Z. Litten[1], Ismene L. Petrakis[2], Tracy Simpson[3], David Oslin, Ismene L. Petrakis[2]
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The prevalent rate of co-occurring post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) is high. Patients suffering from this comorbidity tend to have a more severe clinical impairment, higher rate of psychosocial and medical problems, a higher utilization of health services, higher suicide rate, and lower quality of life. Moreover, Veterans who have experienced combat are at a very high risk for developing PTSD and subsequently, problematic drinking. In this panel session, advances in treatments, especially medications, to treat this population will be presented. Several strategies will be presented including medications and behavioral therapies to treat AUD and/or the underlying psychiatric disorder and new medications that target potentially common neurobiology. Dr. Ismene Petrakis will present results of two studies including a trial that compared noradrenergic vs. serotonergic antidepressant with or without naltrexone and a more recent study of prazosin, an adrenergic α1 antagonist, in Veterans with PTSD and comorbid alcohol dependence. Results indicate that medications that act on the noradrenergic site have the most success. In support of that finding, Dr. Tracy Simpson will present her latest results of prazosin in treating comorbid PTSD and alcohol dependence. In a pilot study, prazosin was effective in reducing the frequency and amount of drinking in this population. Finally, Dr. David Oslin will present his latest findings on a trial of naltrexone and prolonged exposure therapy (PE) for patients with comorbid PTSD and alcohol dependence. Naltrexone successfully reduced the number of drinking days, while the combination of naltrexone and PE has the best drinking outcome 6 months after treatment. In addition, Dr. Oslin will present findings from a second trial that compared the efficacy of motivational enhancement therapy (MET) and PE in Veterans with PTSD and AUD/substances use disorder. Progress in this area is essential if we are to develop effective treatments for this understudied comorbid population.

Learning Objectives:

- Determine the latest treatment approaches for treating individuals with a comorbid PTSD and AUD.
- Determine the latest findings of medications that target the adrenergic and opioid systems.
- Determine the effectiveness of MET and PE therapies in the treatment of PTSD and AUD comorbidity.

INDIVIDUAL ABSTRACT:
PHARMACOTHERAPY OF PATIENTS WITH POST TRAUMATIC STRESS DISORDER (PTSD) AND COMORBID ALCOHOL USE DISORDERS AMONG VETERANS

Ismene L. Petrakis
Yale University School of Medicine

Alcohol dependence (AD) in patients with posttraumatic stress disorder (PTSD) is associated with a worse prognosis and significant psychiatric, medical and social consequences. Several strategies for treating these patients is possible 1) use of medications approved to treat alcohol use disorders 2) use of medications to treat the underlying psychiatric disorder that may be particularly effective in addressing a comorbid substance use disorder or 3) novel medications that target a potentially common neurobiology. Several studies, including one recently concluded study, representing these different strategies will be presented. The studies include a study of the effectiveness of the medications for alcohol use disorders among those with PTSD; a study comparing different antidepressants in Veterans with PTSD and comorbid AD will be presented. In addition, results from a study evaluating the efficacy of prazosin for those with PTSD and comorbid AD will be presented. Future directions of other potential novel compounds will also be discussed.

Learning Objectives:

- Identify and recognize the risk /benefit ratio of medications to treat alcohol dependence in patients with post-traumatic stress disorder.
- Increase awareness of the potential risk/benefit ratio of medications such as antidepressants and prazosin for post-traumatic stress disorder in patients with comorbid alcohol use disorders.

Literature References:

- Petrakis IL, Poling J, Levinson C, Nich C, Carroll K, Ralevski E, Rounsaville B. Naltrexone and Disulfiram in Patients with Alcohol Dependence and Comorbid Post Traumatic Stress Disorder. Biol Psychiat, 2006; 60(7):777-83. PMID: 17008146
- Petrakis IL, Ralevski E, Desai N, Trevisan L, Gueorgeuieva R, Rounsaville B, Krystal JH. Noradrenergic vs. Serotonergic Antidepressant with/without Naltrexone for Veterans with PTSD and Comorbid Alcohol Dependence. Neuropsychopharmacology, 2012; 37:996-1004. PMID: 22089316

INDIVIDUAL ABSTRACT:
PRAZOSIN FOR COMORBID PTSD AND ALCOHOL DEPENDENCE: A PILOT RANDOMIZED CLINICAL TRIAL

Tracy Simpson
VA Puget Sound Health Care System

Background: Alcohol dependence (AD) is a biologically, genetically based disease, yet the majority of clinically accepted treatments are behaviorally or psychosocially based. PTSD and AD commonly co-occur. This comorbidity is associated with more severe clinical impairment, shorter times to relapse, more treatment recidivism, overall greater use of treatment services, and greater treatment costs. Neuropharmacology of alcohol and prazosin: Emerging pre-clinical evidence shows that noradrenergic systems are involved in brain processes relevant to AD, such as arousal, reinforcement, and stress responsivity. However, virtually no work to date has attempted to translate this knowledge into clinically effective biological interventions. We have

adopted the novel, promising strategy of reducing adrenergic activity by blocking noradrenaline binding to post-synaptic α1 receptors via the non-selective, α1 antagonist, prazosin. Preclinical studies have demonstrated that prazosin decreases reinstatement of alcohol consumption, and preliminary clinical data suggest that prazosin reduces alcohol use in humans with AD and reduces PTSD-related nightmares and other symptoms. Prazosin, FDA approved to treat hypertension, typically has few side effects, and is inexpensive. Method: Over an eighteen month period 30 individuals with both AD and PTSD (37% women) with stated goal to abstain from alcohol use were randomized to receive either prazosin or matched placebo for 6 weeks with Medical Management (MM) based on the COMBINE Study procedures. The primary outcomes assessed via a daily Interactive Voice Response (IVR) data collection system were days drinking and number of drinks per day during as well as PTSD symptom severity and craving. Mixed linear regression modeling was used to test for differences in change over time between prazosin+MM vs placebo+MM on alcohol use, craving and PTSD symptoms. Results: With the exception of craving, which was greater in the prazosin+MM group ($p = 0.037$), no baseline differences were detected. Between baseline and week 6, standard drink units (SDUs) per week decreased from an estimated 80.2 (SE = 11.2) to 5.3 (SE = 14.5) in the prazosin group, compared to 50.7 (SE = 11.2) to 29.6 (SE = 11.8) in the placebo group ($chi2(6) = 19.26$, $p = 0.004$). Drinking days per week decreased from an estimated 5.1 (SE =0.6) at baseline to 1.4 (SE = 0.8) at week 6 in the prazosin group, compared to 4.2 (SE = 0.5) at baseline and 4.3 (SE = 0.7) at week 6 in the placebo group ($chi2(6) = 20.00$, $p = 0.003$). Group differences were not detected in change over time on overall PTSD symptoms, PTSD subscales, or craving. Although not significant, differences were seen in study dropout, with 7 (46.7%) prazosin+MM and 4 (26.7%) placebo+MM patients receiving less than 6 weeks of medication. No differences were seen between groups in proportion of patients experiencing adverse events. Public health implications: There is a paucity of safe, tolerable, inexpensive, and efficacious drugs currently available for the treatment of AD and PTSD. Although the results regarding PTSD are disappointing, we do think that prazosin's apparent effect on drinking behavior is important and indicates that prazosin may be an additional pharmacological tool that could help people who are dependent on alcohol to make crucial changes in their lives with regard to their alcohol consumption.

Learning Objectives:

- Understand the effect of prazosin on drinking and PTSD outcomes among dually disordered treatment seeking patients.
- Understand the day to day associations between medication titration and treatment response based on daily Interactive Voice Response (IVR) monitoring data.

Literature References:

- Simpson, T.L., Saxon, A.J; Meredith, C.W., Malte, C.A.; McBride, B.; Ferguson, L.C.; Gross, C.A., Hart, K.L. & Raskind, M.A. (2009). A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcoholism Clinical and Experimental Research, 33, 255-263.
- Simpson, T.L., Galloway, C., Rosenthal, C.F., Bush, K.R., McBride, B., & Kivlahan, D.R. (2010). Telephone monitoring compared with retrospective recall of alcohol use among patients in early recovery. American Journal on Addictions, 20, 63-68.

INDIVIDUAL ABSTRACT:
EFFECTIVE TREATMENT STRATEGIES FOR PATIENTS WITH CONCURRENT PTSD AND ADDICTION

David Oslin
University of Pennsylvania
Addiction comorbid with posttraumatic stress disorder (PTSD) has been found to reduce prognosis for positive treatment outcomes. There are few models of care integrating the treatments for these two disorders. We will present data from two randomized clinical trials integrated PTSD and addiction treatment. The first trial was a randomized control trial of 165 participants with PTSD and Alcohol Dependence. Participants were randomly assigned to (1) prolonged exposure therapy plus naltrexone (100 mg/d), (2) prolonged exposure therapy plus pill placebo, (3) supportive counseling plus naltrexone (100 mg/d), or (4) supportive counseling plus pill placebo. Prolonged exposure therapy was composed of 12 weekly 90-minute sessions followed by 6 biweekly sessions. All participants received supportive counseling. Participants in all 4 treatment groups had large reductions in the percentage of days drinking. However, those who received naltrexone had lower percentages of days drinking than those who received placebo (mean difference, 7.93%; P = .008). There was also a reduction in PTSD symptoms in all 4 groups, but the main effect of prolonged exposure therapy was not statistically significant. Six months after the end of treatment, participants in all 4 groups had increases in percentage of days drinking. However, those in the prolonged exposure therapy plus naltrexone group had the smallest increases. The second trial is a randomized clinical trial of the efficacy and effectiveness of a treatment program consisting of four weekly sessions of motivational enhancement therapy (MET) and 12 weekly sessions of prolonged exposure therapy (PE). Subjects are randomly assigned to receiving both treatments together in an integrated fashion or sequentially with the MET delivered first. To date, we have enrolled 51 Veterans who met criteria for PTSD and an SUD (abuse or dependence) and we have pre- and post-treatment data for 35 Veterans. Pre- to post-treatment analyses of the intent-to-treat (ITT) sample showed a significant reduction in PTSD symptoms as measured by the PTSD Symptom Scale Interview (PSSI; $t(30) = 4.08$, $p < .001$) and a reduction in alcohol use as measured by the Brief Alcohol Monitor (BAM; $t(33) = 3.54$, $p = .001$).Both of these studies demonstrate that treatments for these disorders can be combined and lead to substantial improvements in both conditions.

Learning Objectives:

- Participants will have an appreciation for the clinical complexity of patients presenting with concurrent PTSD and addiction.
- Participants will gain knowledge on the integrated treatment of PTSD and addiction.

Literature References:

- Concurrent naltrexone and prolonged exposure therapy for patients with comorbid alcohol dependence and PTSD: a randomized clinical trial. Foa EB, Yusko DA, McLean CP, Suvak MK, Bux DA Jr, Oslin D, O'Brien CP, Imms P, Riggs DS, Volpicelli J. JAMA. 2013 Aug 7;310(5):488-95. doi: 10.1001/jama.2013.8268.
- Integrated exposure-based therapy for co-occurring posttraumatic stress disorder and substance dependence: a randomized controlled trial. Mills KL, Teesson M, Back SE, Brady KT, Baker AL, Hopwood S, Sannibale C, Barrett EL, Merz S, Rosenfeld J, Ewer PL. JAMA. 2012 Aug 15;308(7):690-9. doi: 10.1001/jama.2012.9071.

PANEL
4:15 PM – 5:45 PM

PANEL OVERVIEW:
NOVEL AND UNDERUTILIZED STRATEGIES TO IMPROVE ADHERENCE AND REDUCE RELAPSE RISK IN SCHIZOPHRENIA

Christoph Correll[1], John M. Kane[1], Adam Hanina[2], Dror Ben-Zeev[3], Nina Schooler[4]
[1]The Zucker Hillside Hospital, Psychiatry Research, North Shore - Long Island Jewish Health System, [2]Ai Cure Technologies, [3]Dartmouth College, [4]SUNY Downstate Medical Center

Maintenance treatment and relapse prevention are arguably the most important goals in the management of schizophrenia. Unfortunately, to date, impending relapse can neither be well predicted nor prevented. One established and very potent predictor of relapse is non-adherence, and both non-adherence and relapse are closely linked to hospitalizations, decreased functioning and, possibly, disease progression. This symposium will focus on the goals and threats, challenges and opportunities in the long-term management of patients with schizophrenia. In particular, this symposium will focus on underutilized as well as novel methods to identify impending relapse, and measuring as well as addressing non-adherence. John Kane, MD, will set the stage by presenting data on the long-term goals in schizophrenia, including response, remission and recovery. He will present up-to date results on relapse and recovery rates in schizophrenia. He will further identify the various obstacles to achieving long-term treatment goals in schizophrenia, including physical and psychiatric comorbidities, residual symptoms, lack of insight, as well as non-adherence. Christoph Correll, M.D., will review the data and recent meta-analyses regarding the maintenance effect of first- and second-generation antipsychotics. Data will be presented for oral and long-acting injectable antipsychotics compared to placebo, and for comparisons oral and in long-acting injectable formulations in randomized controlled, mirror-image and cohort study designs. The effect of trial design, patient populations and comparators will be discussed critically, and patient and prescriber reasons for the low utilization rates of .long-acting injectable antipsychotics will be discussed. Adam Hanina, MBA MPhil, will review different medication adherence monitoring technologies that may be used in patients with schizophrenia ranging from text messaging to microchips-on-pills. He will introduce a novel NIH-funded platform that uses facial recognition on mobile devices to confirm medication adherence in real time. Data from an ongoing phase two schizophrenia trial will be presented to show adoption and usage of this new technology. Finally, he will outline the economics of adoption and the importance of return on investment by introducing the strategy behind stakeholder alignment and incentive structures in the treatment of schizophrenia. Dror Ben-Zeev, M.D., will review data on predictors and early signs of relapse in schizophrenia. He will discuss the difficulties of identifying early signs of impending relapse, which has minimized the success of target and event-driven, enhanced prevention efforts. He will present data from an ongoing Center for Medicaid and Medicare-funded study in which patients utilize smart phones and laptops as means to communicate their symptoms and receive individualized interventions. Moreover, he will present the methodology and design of a recently funded NIMH study in which novel smart phone technology is tested as a means to identify symptomatic exacerbation through analysis of changes in voice and speech patterns.

Learning Objectives:

- Understand the link between non-adherence, its measurement and treatment, and relapse prevention in schizophrenia.
- Familiarize participants with novel technologies that can aide in identifying and managing non-adherence.

INDIVIDUAL ABSTRACT:
RESPONSE, REMISSION AND RECOVERY IN SCHIZOPHRENIA

John M. Kane
The Zucker Hillside Hospital

The goals of treating schizophrenia can be divided into a number of broad domains-response, remission and recovery. Response generally refers to the improvement expected during the treatment of a relapse or exacerbation. Response is often measured by clinicians in a global judgment fashion, but by investigators and clinical "trialists" with the use of quantitative assessment instruments/rating scales. Response is often characterized on a continuum, ranging from none or minimal to moderate or marked. Recent research has focused on early response/non-response after two weeks of treatment as a potential biomarker, with 70% of patients failing to achieve at least minimal response (defined as 20% or greater improvement on a total rating scale score). Such patients are unlikely to achieve the same degree of response, even after 10-12 weeks, as those who do achieve a greater than 20% improvement after two weeks. Remission on the other hand, represents the relative absence of significant signs or symptoms with a minimum time requirement, which has been six months in the most widely applied criteria for schizophrenia (Andreasen et al 2005). The remission criteria can also be applied on a cross-sectional basis, however, in order to measure response in an acute, short term trial, or to characterize a population at one point in time. Recovery generally includes not only a requirement for symptom remission, but a minimal level of functioning, socially and vocationally as well as in self-care. Rates of recovery in schizophrenia have been disappointingly low. For example, in a meta-analysis of 50 studies the median proportion of patients meeting recovery criteria was only 13.5% (25%-75% quintiles: 8.1%-20.0%). While studies from sites in countries with poorer economic status had higher recovery proportions, the generally low recovery rates were not moderated by sex, midpoint of intake period, strictness of the diagnostic criteria, duration of follow-up, or first episode status at baseline (Jääskeläinen et al. 2013).There are a number of factors which reduce the likelihood of recovery ranging from poor insight and high rates of relapse to negative symptoms, cognitive dysfunction, comorbid substance abuse and poor adherence. Together, these factors lead to high relapse rates associated with schizophrenia, which have recently been reviewed (Kane et al. 2013). Non adherence in medication-taking is a major reason for relapses and a key obstacle to remission and recovery, yet at the same time, it is very common among patients with schizophrenia and other psychotic illnesses. Our ability to prevent non-adherence is limited by our ability to measure and to monitor in ways that are not overly intrusive or expensive. The evolution of new technologies provides a window of opportunity to address this challenge.

Learning Objectives:

- To review obstacles to recovery in patients with schizophrenia.
- To discuss the role of non-adherence in medication-taking in reducing rates of response, remission and recovery.

Literature References:

- Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, Veijola J, Miettunen J. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013 Nov;39(6):1296-306.

• Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. World Psychiatry. 2013 Oct;12(3):216-26.

INDIVIDUAL ABSTRACT:
EFFECT OF TRIAL DESIGN, POPULATION AND ILLNESS PHASE ON THE ROLE OF LONG-ACTING INJECTABLE ANTIPSYCHOTICS FOR SIGNALING AND PREVENTING NON-ADHERENCE IN SCHIZOPHRENIA

Christoph Correll
The Zucker Hillside Hospital, Psychiatry Research, North Shore - Long Island Jewish Health System, Glen Oaks, New York, USA

Maintenance treatment and relapse prevention are arguably the most important treatment phases in the management of schizophrenia. Management options include monotherapy with oral antipsychotics (OAPs), adjunctive pharmacologic and non-pharmacologic treatments, long-acting injectable antipsychotics (LAIs), and implantable antipsychotics. Since non-adherence is highly prevalent in schizophrenia and since non-adherence is closely linked with relapses, hospitalizations decreased functioning and, possibly, disease progression, the use of LAIs has long been proposed as an important treatment strategy for the maintenance management of schizophrenia. As there is no gold standard to measuring adherence, LAIs are both a treatment for as well as an objective and immediate measure of non-adherence enabling immediate action when someone does not return for the scheduled injection without precipitous drop of antipsychotic blood levels. However, despite known, high non-adherence rates and increasing options, LAI utilization has remained low in general and much lower in the US than in many other countries. This presentation will review the evidence base regarding the utility of LAIs and their place in the treatment algorithm in the management of schizophrenia. The effect of oral antipsychotics and of LAIs versus placebo for relapse prevention and re-hospitalization will be compared. Furthermore, three complementary sets of meta-analytic evidence for the effectiveness of LAIs versus oral antipsychotics will be reviewed: 1) randomized controlled trials, mirror image studies and cohort studies. The effect of trial design, patient population, illness phase, adherence measures and outcomes, and comparators will be discussed critically. Finally, patient and prescriber reasons for and against LAIs, as well as barriers to the appropriate and earlier use of this treatment option will be examined to capture patients prior to non-adherence.

Learning Objectives:
• Critically discuss the trial results of long-acting injectable antipsychotics compared to placebo and oral antipsychotics depending on trial, patient and treatment characteristics.
• Appreciate the potential role of long-acting injectable antipsychotics in the management of schizophrenia.
• Identify patient, family, prescriber and setting characteristics that influence attitudes in favor and against use of long-acting injectable antipsychotics.

Literature References:
• Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU. Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials. Schizophr Bull. 2013 Jan 2. [Epub ahead of print]

• Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable vs. oral antipsychotics in schizophrenia: A systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry. 2013 Oct;74(10):957-65.
• Kane JM, Kishimoto T, Correll CU. Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. J Clin Epidemiol. 2013 Aug;66(8 Suppl):S37-41.

INDIVIDUAL ABSTRACT:
LEVERAGING NOVEL TECHNOLOGIES TO ENHANCE ADHERENCE
Adam Hanina
Ai Cure Technologies
Adam Hanina, MBA MPhil, will review different medication adherence monitoring technologies that may be used in patients with schizophrenia ranging from text messaging to microchips-on-pills. He will introduce a novel NIH-funded platform that uses facial recognition on mobile devices to confirm medication adherence in real time. Data from an ongoing phase two schizophrenia trial will be presented to show adoption and usage of this new technology. Finally, he will outline the economics of adoption and the importance of ROI by introducing the strategy behind stakeholder alignment and incentive structures in the treatment of schizophrenia.

Learning Objectives:
• Review of different medication adherence monitoring technologies that may be used in patients with schizophrenia.
• Introduce a novel NIH-funded platform that uses facial recognition on mobile devices to confirm medication adherence in real time.
• Outline the economics of adoption and the importance of stakeholder alignment in the treatment of schizophrenia.

Literature References:
• Medication adherence data captured from a Phase 2 schizophrenia clinical trial for a top 10 pharmaceutical company.

INDIVIDUAL ABSTRACT:
TECHNOLOGY-BASED APPROACHES FOR THE DETECTION AND PREVENTION OF RELAPSE IN SCHIZOPHRENIA
Dror Ben-Zeev
Dartmouth College
Schizophrenia develops in approximately 1% of the world's population and is associated with staggeringly high costs. The illness is typically chronic, but not static, and patients vacillate between periods of remission and episodes of symptomatic relapse. Relapses are the chief driver of costly treatments and hospitalizations and increase one's risk for major problems including homelessness, incarceration, victimization, self-injury, and suicide. Relapses do not occur without warning; patients will often experience a host of symptomatic, behavioral, and functional changes days or even weeks before impending psychotic relapse. Detection of these early warning signs would be extremely beneficial, as treatments could be deployed in a time-sensitive manner to prevent full relapse and hospitalization. In the first part of the talk, Dr. Ben-Zeev will provide a brief review of the current state of the science regarding detection of early warning

signs in schizophrenia. In the second, he will present data from the Improving Care Reducing Costs (ICRC) initiative. This large multi-state project is funded by the Center for Medicare and Medicaid Innovation (CMMI) and involves the deployment of several technology-based tools (i.e. a smartphone illness self-management system, laptop-based coping with voices program, and a daily support website for patients and family members) to help prevent re-hospitalization in over 600 high-risk patients with schizophrenia. In the 3-year project, each patient works with a technology/ health coach that helps them track and report their symptoms, use smartphone and web-based applications to manage their illness, and increase medication adherence in order to reduce relapse rates. The presentation will end with a conceptual overview of a novel mobile system that is being developed with support from NIH's EUREKA program, specifically designed to encourage innovative, high-risk, and potentially ground-breaking research. The goal of the project is to develop and evaluate a mobile technology that uses smartphone-embedded sensors (i.e. microphone, accelerometer, GPS, light sensor) coupled with computerized self-reports, to track a range of behaviors that are relevant to relapse in schizophrenia. Using machine learning techniques, the system leverages passively collected behavioral data and patient self-reported clinical updates to generate personalized early warning models. Once the system detects behaviors that are consistent with the individual's unique "relapse signature", both the user and their clinical team are notified, triggering outreach and more intensive services. If successful, an effective multi-modal mobile monitoring, early detection, and intervention system can change when, how, and to what effect treatments are delivered, allowing for a paradigmatic shift from largely reactive to preemptive care for psychotic episodes in schizophrenia.

Learning Objectives:

- Review of the state of the science in detection of early warning signs in schizophrenia.
- Learn about the use of mobile technologies such as cellular phones and smartphones to monitor illness and facilitate relapse prevention efforts.

Literature References:

- Ben-Zeev, D., Kaiser, S.M., Brenner, C.J., Begale, M., Duffecy, J., Mohr, D.C. (2013). Development and Usability Testing of FOCUS: A Smartphone System for Self-Management of Schizophrenia. Psychiatric Rehabilitation Journal. ePub ahead of print, doi: 10.1037/prj0000019.
- Ben-Zeev, D., Davis, K., Kaiser, S., Krzos, I., & Drake, R.E. (2013). Mobile technologies among people with serious mental illness: Opportunities for future services. Administration and Policy in Mental Health and Mental Health Services Research, 40 (4) 340-343.

PANEL
4:15 PM – 5:45 PM

PANEL OVERVIEW:
PLACEBO RESPONSE, RESPONSE VARIANCE AND ANTIDEPRESSANT-PLACEBO DIFFERENCES IN RECENT ANTIDEPRESSANT CLINICAL TRIALS BASED ON THREE PATIENT INTERVIEW MODELS

Arif Khan[1], Steven D. Targum[2], Michael Detke[3], Walter Brown[4]
[1]Northwest Clinical Research Center, [2]Clintara LLC, [3]Clinical Professor of Psychiatry, Indiana University, [4]Brown University

In response to the high failure rate of antidepressant clinical trials due to a high magnitude of placebo response and its variance, some significant modifications have been made to the

techniques used in gathering patient interview data. Although many recent antidepressant trials continue to be conducted using the traditional model of semi-structured, open ended psychiatric interviews, several trials are being conducted using recently developed structured psychiatric interviews that are taped and either conducted or appraised by 'central' raters. Dr. Targum and his group have conducted site-independent reviews using audio-digital pen recordings of site-based interviews to obtain "dual" blinded scoring of key ratings interviews. In his panel presentation, Dr. Targum will describe and explore several issues that may compel a clinical trial to failure including inappropriate subject selection, pre-randomization ratings inflation, insufficient interviews, "dual" scoring discordance, and marked variability of interview length. He will present data from several recent clinical trials across the CNS spectrum that demonstrate that surveillance systems operating as quality assurance strategies can identify rater outliers, affirm well-trained site-based raters, and ultimately improve site-based data integrity. Dr. Detke will present data from the use of blinded, independent, remote ratings in psychiatric clinical trials. In this methodology, small cohorts of raters interview the subjects by teleconference or videoconference. He will present data on the validity of such approaches in comparison to traditional face-to-face interviews, review data suggesting some of the limitations of face-to-face interviewing, and review data from several recent clinical trials with head-to-head comparisons of face-to-face and blinded, independent remote ratings which assess the effects of these methodologies on both placebo response and drug-placebo separation. Dr. Khan will present data from a single antidepressant clinical trial site from the past twenty years. Data presented will include the mean decrease in depressive symptoms of patients assigned to placebo and variance in placebo response in trials conducted using the traditional methods as well as data from a recent set of trials that used other models including Structured Interview for the Montgomery-Asberg Depression Rating scale (SIGMA) rating interviews, Rater Applied Performance Scale (RAPS) review of raters and outside surveillance. Dr. Brown will facilitate a discussion for the session.

Learning Objectives:

- These data are being presented to help design future antidepressant clinical trials.
- Understand the mechanisms that may influence antidepressant clinical trial outcomes.

INDIVIDUAL ABSTRACT:
EXAMINING THE UTILITY AND FUTILITY OF SURVEILLANCE STRATEGIES FOR CNS TRIALS

Steven D. Targum
Clintara LLC

Signal detection relies are ratings consistency throughout a clinical trial. In turn, ratings consistency may be compromised by site-based raters who feel time pressure at the clinic, conduct incomplete assessments, or are prone to scoring inaccuracy. Similarly, subject compliance may vary at each visit by changing motivation to participate and/or unrelated extraneous personal events that may affect their perceptions and reporting of psychiatric symptoms. We have used audio-digital pen recordings of site-based interviews done in clinical trials across the CNS spectrum. As part of the surveillance strategy, "dual" scoring of key ratings are done by site-independent clinical reviewers who are blinded to study visit, study site, and protocol specifics. Our thesis has been that a well-executed surveillance strategy can facilitate site-based data integrity and optimize ratings precision. In this panel presentation, we will describe and explore several issues that have been identified by site-independent reviews of over

3000 site-independent assessments that may compel a clinical trial to failure. These issues include inappropriate subject selection, pre-randomization ratings inflation to achieve entry threshold criteria, insufficient interviews, and marked variability of interview length. In addition, we will present data from several recent clinical trials that demonstrate that surveillance systems operating as quality assurance strategies can identify rater outliers and ultimately affirm well-trained site-based raters.

Learning Objectives:

- The understand the inherent challenges that may affect study success in CNS clinical trials.
- The explore the specific conflicts about data consistency encountered by site-based raters and patients who participate in CNS clinical trials.

Literature References:

- Targum SD, Wedel PC, Bleicher LS, Busner J, Daniel DS, Robinson J, Rauh P, Barlow C. A comparative analysis of centralized, site-based, and patient ratings in a clinical trial of Major Depressive Disorder. Journal Psychiatric Research. 47: 944-954, 2013.
- Targum, SD, Little, JA, Lopez, E, DeMartinis, N, Rapaport, M, Ereshefsky, L. Application of external review for subject selection in a schizophrenia trial. J Clin Psychopharmacol., 32 (2): 825-826, 2012.

INDIVIDUAL ABSTRACT:

THE USE OF BLINDED, INDEPENDENT, REMOTE RATINGS IN PSYCHATRIC CLINICAL TRIALS: THE GOOD, THE BAD, AND THE APPROPRIATE SITUATION

Michael Detke

Clinical Professor of Psychiatry, Indiana University

Placebo response and drug-placebo separation in MDD clinical trials have always been challenging, and have gotten more so recently (Khin, 2011). The challenges are many: limited knowledge of pathophysiology resulting in drugs that may be suboptimal in efficacy and/or safety; limited knowledge of the nosology of what is likely a very heterogeneous group of disorders, resulting in further limitation on the efficacy and safety of drugs and other treatments; protocol criteria and outcomes that are subjective, leading to the enrollment of some inappropriate subjects and inaccurate ratings at times. This presentation will focus primarily on the last issue. We will review data on some of the limitations of face-to-face interviewing, such as enrollment bias through baseline score inflation and diagnostic "inflation", as well as the potential for poor quality interviews without oversight, and finally such phenomena as therapeutic alliance and expectation bias. One approach to minimizing the variance and biases introduced by traditional face-to-face clinical assessments is to employ blinded, independent, remote ratings. This is the quality standard mandated by the FDA & EMA in many other therapeutic areas with subjective assessments, such as the interpretation of imaging studies or special tests like echocardiograms. In this methodology, small cohorts of raters interview the subjects directly and live, by teleconference or videoconference. We will review data on the validity of such approaches in comparison to traditional face-to-face interviews. We will review data indicating that fewer raters can be employed, which is one way to reduce variance. We will review data on the use of alternating raters, and its impact on therapeutic alliance and expectation bias. Alternating raters underscores the need for training and standardization across the rater cohort, which is important regardless. Finally, we will analyze the outcomes from recent clinical trials with head-to-head comparisons of face-to-face and blinded, independent remote ratings

which assess the effects of these methodologies on both placebo response and drug-placebo separation. In general, these data show lower placebo response and greater drug-placebo separation with remote ratings (the "good"). Lastly, we will discuss some of the challenges of using remote raters (the "bad") and some clinical trial situations in which they are more or less well-suited (the "appropriate").

Learning Objectives:

- There are several sources of potential error in clinical trials, both in subject selection and in outcomes assessment. There are many causes of bias and variance in these.
- One approach to addressing bias and variance is the use of remote independent ratings. There are strengths and weaknesses to this approach. Other approaches, along with strengths and weaknesses, will be covered in the other presentations in this session.

Literature References:

- Khin Ni A. et al. (2011). Exploratory Analyses of Efficacy Data From Major Depressive Disorder Trials Submitted to the US Food and Drug Administration in Support of New Drug Applications. Journal of Clinical Psychiatry. 72:4, 464-472.
- Kobak, KA et al. (2010). Site versus Centralized Raters in a Clinical Depression Trial: Impact on Patient Selection and Placebo Response. Journal of Clinical Psychopharmacology, 30 (2) 193-1972

INDIVIDUAL ABSTRACT:

MAGNITUDE OF PLACEBO RESPONSE AND RESPONSE VARIANCE IN ANTIDEPRESSANT CLINICAL TRIALS USING ENHANCED INTERVIEWS TECHNIQUES COMPARED TO TRADITIONAL RATING INTERVIEWS

Arif Khan

Northwest Clinical Research Center

The high failure rate of antidepressant clinical trials, in part due to a high magnitude of placebo response and its variance, has led use of enhanced interview techniques in some of the recent antidepressant clinical trials. Such techniques include structured interviews for the Montgomery-Asberg Depression Rating Scale (SIGMA)1, 'central ratings' conducted via video or audio-taped interviews or with 'site raters' that are audio-taped to provide rater surveillance using the Rater Applied Performance Scale (RAPS)2. Another technique has been to audio-tape depressed interview techniques using a pen that is a tape-recorder. Although these techniques have been implemented in some of the trials, a considerable number of antidepressant clinical trials carried out in recent years have continued to use the standard method of patient interviews. These are semi-structured, open ended, conversational and empathic interviews to obtain both verbal and non-verbal data. So far, the data are sparse to evaluate if the newer techniques actually reduce the magnitude of placebo response and its variance. In this presentation, we will present data from the Northwest Clinical Research Center (NWCRC) that has been involved in Phase II and Phase III antidepressant clinical trials for 20 years. The data will include results from trials conducted between 1996 and 2004 that examine the magnitude of placebo response and its variance. Furthermore, we will present data from ten antidepressant clinical trials that were conducted between 2008 and 2012. Four of these included standard psychiatric interview techniques and six that included at least two different methods of enhanced interview techniques. The total sample consists of 160 depressed patients assigned to placebo.

Learning Objectives:
- Evaluate if recently introduced depression interviews that are intended to increase interview reliability reduce the placebo response in antidepressant clinical trials.
- Understand potential mechanisms that influence the placebo response.

Literature References:

- Williams JW & Kobak K. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). British Journal of Psychiatry 2008; 192:52-58.
- Lipsitz J, Kobak K, Feiger A, Sikich D, Moroz G, Engelhardt N. The rater applied performance scale: development and reliability. Psychiatry Research 2004; 127:147-155.

Tuesday, June 17, 2014

PLENARY SESSION
8:30 AM – 10:00 AM

REGULATORY PLENARY: FDA REGULATORY SCIENCE INITIATIVES: A BRIEF UPDATE

Chair: *Ni A. Khin, M.D., U.S. Food and Drug Administration*
Speakers: *Celia Winchell, M.D., Food and Drug Administration*
Silvana Borges, M.D., Food and Drug Administration
This session will provide updates on regulatory initiatives from the US Food and Drug Administration (FDA). Dr. Ni Khin will give a brief overview of the joint FDA initiative with European Medicines Agency (EMA) to ensure data quality in clinical trials and good clinical practice compliance. Dr. Celia Winchell from FDA's Division of Anesthesia and Analgesia Products (DAAP) will discuss the challenges of determining efficacy endpoints in clinical trials for addiction treatment drugs. Specifically, she will discuss how DAAP identified a pattern of alcohol use as an alternative endpoint to complete abstinence based on recent analyses of data. Dr. Silvana Borges from FDA's Division of Psychiatry Products will present preliminary findings regarding use of active controls in depression trials. There will be an informal discussion with the audience on these selected topics as well as other regulatory issues of common interest within this context.

ASCP LIFETIME AWARDEE PRESENTATION
10:15 AM – 11:15 AM

BRIDGING THE CHASM BETWEEN RESEARCH AND PRACTICE
John Rush
Duke-National University of Singapore (Duke-NUS)
Patient centered research and comparative effectiveness research address practical issues that aim at addressing patients' concerns or choices among treatments, respectively. In addition to these important objectives, clinicians need to better understand how to deliver each treatment; to

whom to deliver (or not) particular treatments; when to discontinue, switch, or augment a specific treatment; and for whom which specific treatment sequences are indicated. This presentation discusses practical, simple, efficient research design, measurement and analytic options, that could address these important clinical knowledge gaps with the aim of improving patient outcomes and treatment cost efficiencies.

PANEL
1:00 PM – 2:30 PM

PANEL OVERVIEW:
INFLAMMATION AND INSULIN RESISTANCE: IMPLICATIONS FOR PATHOPHYSIOLOGY AND TREATMENT

David Kemp[1], Jess G. Fiedorowicz[2], Jonathan Savitz[3], Flavio Kapczinski[4], Madhukar Trivedi[5]
[1]Case Western Reserve University, [2]University of Iowa, [3]Laureate Institute for Brain Research, [4]Flavio Pereira Kapczinski, [5]UT Southwestern

Recent research has identified a link between cardio metabolic illnesses and mood symptoms. Insulin resistance and other cardio metabolic risk factors predict increased risk of depression and decreased response to antidepressant and mood stabilizer treatments. This panel symposium will present new findings implicating inflammation, adipocytokines, and oxidative stress to the pathophysiology of mood states and discuss the role of anti-inflammatory and insulin-sensitizing agents as potential treatments for mood disorders. Results will be presented from an open-label proof-of-concept study evaluating the effects of pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist with insulin sensitizing properties, on bipolar depression symptom severity. This study found significant improvement to occur in depression severity with pioglitazone treatment. Moreover, a positive correlation was identified between reduction in depression severity and decreases in levels of interleukin-6 and adiponectin. Data on the relationship between cytokines and damage-associated molecular patterns (DAMPs) by mood state will also be presented from two separate samples of patients and controls. These immunogenic markers were identified to become silent during interepisode periods and represent proxies of peripheral toxicity and illness activity. Specifically, higher levels of ccf DNA (nuclear (n)DNA ($p < 0.0001$) and mitochondrial (mt)DNA ($p = 0.032$), as well as HSP70 ($p = 0.02$) were found in drug free bipolar patients compared to healthy controls . After pharmacological treatment, ccf nDNA ($p = 0.013$) and HSPs levels ($p = 0.025$) decreased in those patients that achieved clinical remission. In addition to bipolar disorder, recent findings relating inflammation to brain structure and function will be presented from a population with major depressive disorder (MDD). It was recently discovered that the ratios of kynurenic acid (KA) to 3-hydroxykynurenine (3HK) and KA/quinolinic acid (QA), putative neuroprotective indices, were lower in an unmedicated MDD group relative to a healthy control group, and that within the MDD group, the ratio of KA/QA was inversely correlated with the concentration of IL1RA, a proxy measure of IL1β. Further, in the MDD group, the KA/QA ratio was positively correlated with total hippocampal volume and total amygdala volume. These results raise the possibility that immune dysregulation predisposes to mood disorders via its effect on glutamatergic signaling such that abnormal NMDA receptor signaling may be the unifying mechanism underlying the glutamate and inflammation hypotheses of depression. In summary, the panel will focus on inflammatory cytokines and indicators of cell death or apoptosis that may represent

useful biomarkers for assessing burden of disease in patients with mood disorders as well as targets for novel antidepressant treatments.

Learning Objectives:

- To appreciate the role of inflammation and insulin resistance in the pathophysiology of mood disorders.
- To understand the implications of inflammatory and cardiometabolic biomarkers on illness activity in bipolar disorder and recognize potential novel neurobiological targets for treating depression.

INDIVIDUAL ABSTRACT:
PPAR-γ AGONISM AS A MODULATOR OF MOOD: PROOF-OF-CONCEPT FOR PIOGLITAZONE IN BIPOLAR DEPRESSION

David Kemp
Case Western Reserve University

Insulin resistance and other cardiometabolic risk factors predict increased risk of depression and decreased response to antidepressant and mood stabilizer treatments. Several inflammatory biomarkers, including highly-sensitive C-reactive protein (hs-CRP) and Interleukin-6 (IL-6), are elevated in both cardiometabolic illness and bipolar disorder, and may contribute to the pathophysiology of depressed mood. Inflammatory cytokines have also been shown to inhibit neurogenesis through the activation of nuclear factor κβ, a pathway concurrently implicated in the pathogenesis of hepatic insulin resistance. Pioglitazone is an insulin sensitizer commonly used in the treatment of type-2 diabetes that reduces insulin resistance by activating peroxisome proliferator activated receptors (PPARs), with greatest specificity for PPAR-γ. Central nervous system PPAR-γ receptors appear to regulate insulin sensitizing effects in peripheral tissues and have been shown in animal models to have antidepressant-like effects. In an open-label, proof-of-concept study, we tested whether administration of an insulin-sensitizing PPAR-γ agonist could reduce bipolar depression symptom severity. Fifty patients with bipolar disorder (I, II, or not otherwise specified) and metabolic syndrome/insulin resistance who were currently depressed (Quick Inventory of Depressive Symptoms total score >= 16) despite an adequate trial of a mood stabilizer received adjunctive treatment with the PPAR-γ agonist pioglitazone (15-30 mg/d) for 8 weeks. Pioglitazone treatment was associated with a decrease in the total Inventory of Depressive Symptomatology (IDS-C30) score from 38.8±1.6 at baseline to 23.8±1.8 at week 8 ($p<.001$). A significant decrease occurred in levels of IL-6 (-0.32; $p=.04$), while concentrations of adiponectin, an adipocyte-derived hormone with antidiabetic and insulin-sensitizing properties, significantly increased (6.02; $p<.001$). In addition, a significant correlation was observed between improvement in IDS-C30 score and change in IL-6 ($r=0.39$, $p=.02$) and adiponectin ($r=0.47$, $p=.005$). Recent studies have identified reduced levels of adiponectin in human subjects with major depression, while in animal models, disruption of the adipocytokine signaling pathway appears to be a critical component of the manifestation of depressive-like behaviors. Through reducing inflammation and increasing adiponectin concentrations, PPAR-γ agonism may represent a novel mechanism to modulate mood. In conjunction with the University of Kentucky, we also tested the cognitive effects of a novel brain-penetrable selective dual PPARα/γ agonist, DSP-8658, in aged rats. DSP-8658 is currently in clinical development for the treatment of type-2 diabetes and has been shown to suppress inflammatory gene expression. Results will be briefly presented on tests of learning and memory in aged F344 rats.

DSP-8658 had negative consequences on learning, but not on memory components of the Morris water maze and active avoidance task.

Learning Objectives:

- Understand the action of peroxisome proliferator-activated receptor-gamma agonists on insulin sensitivity, inflammation, and mood.
- Describe the effects of pioglitazone on reducing depressive symptom severity in bipolar disorder and specify potential neurobiological mediators of the observed antidepressant response.

Literature References:

- Kemp DE, Ismail-Beigi F, Ganocy SJ, Conroy C, Gao K, Obral S, Fein E, Findling RL, Calabrese JR.Use of insulin sensitizers for the treatment of major depressive disorder: a pilot study of pioglitazone for major depression accompanied by abdominal obesity. J Affect Disord. 2012 Feb;136(3):1164-73.
- Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS.Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry. 2009 Aug;70(8):1078-90.

INDIVIDUAL ABSTRACT:
TRAIT AND STATE PATTERNS OF INFLAMMATORY BIOMARKERS IN BIPOLAR DISORDER

Jess G. Fiedorowicz
University of Iowa

Bipolar disorder is characterized by episodic fluctuations in mood, activity, and sleep lasting weeks per months and carries with it substantive morbidity and mortality burden. The disorder is also highly hereditable, yet there remain but a very limited mechanistic insight into the factors which contribute to its etiology and the pathogenesis of mood episodes. The most consistent neuroimaging finding seen in bipolar disorder involves a greater prevalence of white matter hyperintensities (WMH). These WMH are seen 2.5 times as often as would be expected from healthy controls and it has been suggested that these lesions may occur secondary to inflammation.1,2 Abnormalities in peripheral inflammatory markers with bipolar have been commonly reported in case control studies3,4 although it is not clear whether these markers change in response to state or are trait markers elevated in a subset of individuals with bipolar disorder. This presentation will review the literature related to inflammation in bipolar disorder and present new data which assesses the profile of inflammatory biomarkers across mood states in bipolar disorder and in comparison to healthy controls.

Learning Objectives:

- To appreciate the potential role of inflammation in the pathogenesis of mood disorders.
- To understand the neurobiological links between mood states and inflammation.

Literature References:

- Mahon K, Burdick KE, Szeszko PR. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neuroscience and biobehavioral reviews. Mar 2010;34(4):533-554.
- Ahn KH, Lyoo IK, Lee HK, et al. White matter hyperintensities in subjects with bipolar disorder. Psychiatry and clinical neurosciences. Oct 2004;58(5):516-521.
- do Prado CH, Rizzo LB, Wieck A, et al. Reduced regulatory T cells are associated with higher

levels of Th1/TH17 cytokines and activated MAPK in type 1 bipolar disorder. Psychoneuroendocrinology. May 2013;38(5):667-676.
• Tsai SY, Chung KH, Wu JY, Kuo CJ, Lee HC, Huang SH. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. Journal of affective disorders. Jan 2012;136(1-2):110-116.

INDIVIDUAL ABSTRACT:
ASSOCIATION BETWEEN KYNURENINE-PATHWAY METABOLITES AND GRAY MATTER VOLUMES OF THE HIPPOCAMPUS AND AMYGDALA IN PATIENTS WITH MOOD DISORDERS

Jonathan Savitz
Laureate Institute for Brain Research

Major Depressive Disorder (MDD) has been associated with reductions in hippocampal and amygdalar volume that are thought to reflect dendritic atrophy and/or decreases in neurogenesis. Some patients with mood disorders display elevated levels of pro-inflammatory cytokines such as IL1β and TNF which increase the formation of kynurenine (KYN) pathway metabolites, including kynurenic acid (KA), a potentially neuroprotective antagonist of NMDA receptors, 3-hydroxykynurenine (3HK), a free radical generator, and quinolinic acid (QA), an NMDA agonist and potential neurotoxin. Whereas an association between molecular markers of inflammation and brain structure and/or function has been found in animal models of depression, the relationship between the peripheral concentrations of kynurenine-pathway metabolites and morphometric MRI abnormalities in mood disorders remains unclear. Here I will present data showing that the ratios of KA/3HK and KA/QA, putative neuroprotective indices, were lower in an unmedicated MDD group relative to a healthy control group, and that within the MDD group, KA/QA was inversely correlated with the concentration of IL1RA, a proxy measure of IL1β. Further, in the MDD group, the KA/QA ratio was positively correlated with total hippocampal volume and total amygdala volume. Secondly, I will present data from an independent sample of unmedicated subjects with MDD, medicated subjects with MDD, and healthy controls both to replicate the original finding and to examine the effects of medication on the relationship between neuromorphometric abnormalities and peripheral immune markers. Since both KA and QA affect glutamate release, our results raise the possibility that immune dysregulation predisposes to mood disorders via its effect on glutamatergic signaling such that abnormal NMDA receptor signaling may be the unifying mechanism underlying the glutamate and inflammation hypotheses of depression.

Learning Objectives:
• The kynurenine theory of depression.
• The potential relationship between immunological and glutamatergic function.

Literature References:
• Dantzer R, O'Connor JC, Lawson MA, Kelley KW (2011). Inflammation-associated depression: from serotonin to kynurenine. Psychoneuroendocrinology 36(3): 426-436.
• Miller AH (2013). Conceptual confluence: the kynurenine pathway as a common target for ketamine and the convergence of the inflammation and glutamate hypotheses of depression. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology 38(9): 1607-1608.

INDIVIDUAL ABSTRACT:
BIOMARKERS OF ILLNESS ACTIVITY IN BIPOLAR DISORDER

Flavio Kapczinski
Federal University of Rio Grande do Sul

Background: Damage-associated molecular patterns (DAMPs) are a product of cell death (necrosis of apoptosis) and are highly immunogenic. Increased levels of early apoptosis have been recently demonstrated in bipolar disorders (BD), but no study so far has examined DAMPs levels in these patients. The aim of this study was to assess serum levels of DAMPs in drug-free BD patients and changes on these biomarkers after pharmacological treatment. Methods: Thirty six drug-free BD patients in acute episode (mania/mixed or depression) and 55 matched healthy controls were recruited. Blood samples were collected at baseline and every week during a 16-week follow-up period among patients. Results: Higher levels of ccf DNA (nuclear (n) DNA ($p < 0.0001$) and mitochondrial (mt) DNA ($p = 0.032$), as well as HSP70 ($p = 0.02$) were found in drug free bipolar patients compared to healthy controls. After pharmacological treatment, ccf DNA ($p = 0.013$) and HSPs levels ($p = 0.0205$) decreased in those patients that achieved clinical remission. Conclusion: DAMPs seem to be altered in bipolar patients during acute episode. Those patients who achieve remission tend to normalize the observed blood alterations. The present findings may be linked to the inflammatory activity previously describe among bipolar patients, particularly during symptomatic periods.

Learning Objectives:
- Understand about the origins of inflammation in Bipolar Disorder.
- Understand about the relationship between stress and mitochondrial function.

Literature References:
- Manfredi AA et al. (2010). The New England Journal of Medicine, 362 (22): 2132-34.
- Zhang Q et al (2010). Nature, 464 (7285): 104-107.

PANEL
1:00 PM – 2:30 PM

PANEL OVERVIEW:
LONG ACTING INJECTABLE ANTIPSYCHOTICS: PERSPECTIVES ON THEIR ROLE IN SCHIZOPHRENIA TREATMENT

Taishiro Kishimoto[1], Nina R Schooler[2], Joseph P. McEvoy[3], John M. Kane[4]
[1]Keio University School of Medicine, Department of Psychiatry, [2]SUNY Downstate Medical Center, [3]Georgia Regents University, [4]The Zucker Hillside Hospital

For many decades the only available long-acting antipsychotics in the United Stated were fluphenazine and haloperidol decanoate. In 2003 this changed when risperidone microspheres became available. Since then three other LAI antipsychotics have become available for prescription in the US. Before the emergence of the newer LAI antipsychotics, the place of LAIs in the treatment armamentarium had been largely confined to patients who had demonstrated that medication non-adherence played an important part in their course and outcome. Development of these newer agents and their availability has sparked a new wave of interest in LAI treatment. Studies with a wide range of patient populations utilizing a variety of designs ranging from placebo-controlled RCTS through randomized but open label studies to mirror-image and other epidemiologically based evaluations have been conducted. A number of LAI-oral randomized

comparisons, mostly of LAI-risperidone (LAI-R), have not found the hypothesized significant advantaged for the LAI. This panel will consider the role of LAIs based on a wide range of data. Kishimoto will evaluate the available data on oral to LAI comparisons to that used varying methods to determine effects in terms of effect size – a metric that can be applied across designs. Schooler will present a secondary analysis of data from a large trial that compared oral to LAI-R and consider specific design features that may contribute to difficulty in detecting hypothesized effects in a randomized controlled trial. Finally, McEvoy will present data that compare first-generation LAIs (represented by haloperidol) to second a second-generation LAI (paliperidone). All of these presentations will contribute to consideration of the role of LAIs in the clinical treatment armamentarium by Kane, members of the panel and the audience.

Learning Objectives:

- Understand results of studies comparing long-acting Injectable (LAI) antipsychotics and studies comparing LAIs to oral medications.
- Evaluate the characteristics of study designs and how they contribute to the ability to detect clinical effects of long-acting antipsychotics.
- Evaluate the potential role of LAI medications in treatment of schizophrenia based on trial and other data

INDIVIDUAL ABSTRACT:
LONG ACTING INJECTABLE VS. ORAL ANTIPSYCHOTICS FOR SCHIZOPHRENIA: META-ANALYTIC CONSIDERATION OF THE TRUE EFFECT SIZE BY THE STUDY DESIGNS

Taishiro Kishimoto
Keio University School of Medicine, Department of Psychiatry

Purpose: High non-adherence rates in schizophrenia can limit the efficacy of pharmacotherapy, therefore, the use of long-acting injectable antipsychotics (LAIs) is considered to be an important treatment option. There have been a variety of reports examining the comparative effectiveness of LAIs verses oral antipsychotics (OAPs). Such studies can be categorized into 3 designs, namely, randomized controlled studies (RCTs), mirror image studies (where the data before and after initiation of LAIs were compared), and naturalistic cohort studies. In order to understand the impact of study design on the effect sizes of LAIs, we have conducted meta-analyses of three study designs comparing LAIs versus OAPs. Methods: Systematic review/meta-analysis was conducted on RCTs [Kishimoto et al. Schizophrenia Bulletin 2013], mirror-image studies [Kishimoto et al. Journal of Clinical Psychiatry 2013] and naturalistic cohort studies comparing LAIs and OAPs. Studies were required to last ≥6 months on each drug and to report relapse-related outcomes. Primary outcomes were either relapse or hospitalization. Pooled relative risks(RR) together with their 95% confidence intervals (CIs) were calculated, using random-effects model. Results: A total of69 studies were identified and meta-analyzed (RCTs: 21 studies, n=5,176; mirror-image studies: 25 studies, n=5,940; naturalistic cohort studies: 33 studies, n=16,668). Across RCTs, LAIs were not significantly superior to OAPs in preventing hospitalization (risk ratio=0.93, 95%CI: 0.80-1.08, p=0.35), whereas, across mirror-image studies, LAIs showed strong superiority over OAPs (RR=0.43, 95%CI: 0.35-0.53, p<0.001). On the other hand, across naturalistic cohort studies, effect sizes of studies varied widely and there was strong heterogeneity. The difference between study groups were significant (Q-value=39.29, df=2, p<0.001). Although information was limited, there seemed to be no outstanding differences in terms of study designs(e.g. medication, dosage) across the reports, but some

patient characteristics as well as procedural differences existed (e.g. age, informed consent, assessments).Conclusion: The results of the three study designs were in strong contrast with each other. Substantial cohort differences may account for the different results in that 1) patients in RCTs are likely to be more adherent, 2) patients in non-RCT (mirror image study, naturalistic cohort study) are mostly LAI-targeted populations in clinical practice that are likely to be non-adherent, 3) patients in the oral arm in naturalistic cohort studies are likely to be more adherent than patients on LAIs. Each study design has its limitation, and one needs to be thoughtful as to how to best utilize the evidence. Future RCTs may benefit from more closely replicating routine clinical circumstances. True large simple trials or two-way-mirror-image studies (oral to LAI, LAI to oral) might be another option.

Learning Objectives:

- To understand the impact of study design on results of antipsychotic long acting injection studies.
- To understand the complexity and the difficulty of designing long acting injection studies.

Literature References:

- Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU. Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials. Schizophr Bull. 2013 Jan 2. [Epub ahead of print]
- Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry. 2013 Oct;74(10):957-65.

INDIVIDUAL ABSTRACT:
PROACTIVE: EXPLORING LONGITUDINAL COURSE TO UNDERSTAND TREATMENT OUTCOMES IN LAI - ORAL COMPARISONS

Nina R Schooler
SUNY Downstate Medical Center

The PROACTIVE study, an eight site randomized clinical trial (RCT) comparing the LAI risperidone (LAI-R) to oral second generation oral antipsychotics (ORAL) in schizophrenia and schizoaffective outpatients, found no significant differences between treatments in time to relapse or re-hospitalization during treatment exposure of up to 30 months (Schooler et al 2011). This finding is congruent with the results of the study by Rosenheck and colleagues (2011). Our findings generalize from a largely male Veterans Affairs (VA) sample to a broader US context and is consistent with findings internationally. Does the absence of statistically significant differences allow us to conclude that oral and injectable medications confer equal benefit in the long term treatment of schizophrenia? This presentation will address this question with data from the PROACTIVE RCT and will also review trial characteristics that may contribute to reduced likelihood of detecting treatment effects PROACTIVE included blinded psychopathology assessments by central raters every three months and biweekly assessments by on-site raters. We found significant differences based on blinded ratings favoring LAI-R in the BPRS Total Score and BPRS psychosis cluster (Schooler 2011). We now explore this difference. We used a narrow definition of psychotic symptoms and examined whether absence of psychotic symptoms accounted for the differences. Cases were dichotomously classified as having either no psychotic symptoms or any. The proportion of such ratings increased over time for the RLAI group (20%

to 39%) compared to the ORAL group (22% to 23%) (Treatment X Visit F=1602, df 1, 1739, p=0001). This difference would not be reflected in an assessment of relapse which measures symptom increase rather than decrease. Other characteristics of the PROACTIVE trial may have contributed to an inability to detect a difference in time to relapse if a true difference exists. All subjects consented to research participation and to treatment randomization. Following randomization, seven LAI-R subjects and two ORAL subjects never received treatment. In the LAI-R arm there was only one treatment option whereas in the ORAL arm patients who had a sub-optimal response to the first oral antipsychotic could be offered others and still remain in the study. Subjects in both treatment arms were seen every two weeks. This is far more frequent than clinical visit frequency for patients receiving oral prescription medication. Visits included a clinical assessment of symptoms. Oral medication was dispensed at these biweekly visits which further increased comparability to the injectable treatment arm but further differentiated the oral condition from usual outpatient clinical care for schizophrenia. On balance, data from the PROACTIVE RCT suggest that for the population of patients included in such studies the benefits of LAI treatment may lie in increasing the likelihood of an absence of psychotic symptoms over time rather than in preventing increase of symptoms to the level of frank relapse. This may be because this population represents more adherent patients for whom oral medication prescribed and administered under optimal clinical conditions serve well to prevent relapse and re-hospitalization.

Learning Objectives:

- Recognize characteristics of RCTs of LAi medications that may be relevant in understanding trial results.
- Understand the value of secondary post-hoc analyses in clarifying the results of the PROACTIVE RCT comparing risperidone LAi and oral antispychotics I.

Literature References:

- Schooler NR, Buckley PF, Mintz J, Goff DC, Kopelowicz A, Lauriello J, Manschreck TC, MendelowitzAJ, Miller DD, Wilson D, Bustillo JR, Severe JB, Kane JM. PROACTIVE: Initial Results of an RCT Comparing Long-acting Injectable Risperidone to 2nd Generation Oral Antipsychotics
- Abstract Neuropsychopharmacol 2011 S104-105. Rosenheck RA, Krystal JH, Lew R et al. Long-Acting Risperidone and OralAntipsychotics in Unstable Schizophrenia. New Engl J Med: 2011:364; 842-851.

INDIVIDUAL ABSTRACT:
A COMPARISON OF LONG-ACTING ANTIPSYCHOTIC MEDICATIONS FOR SCHIZOPHRENIA (ACLAIMS)

Joseph P. McEvoy
Georgia Regents University

Haloperidol decanoate (HD) and paliperidone palmitate (PP) are long-acting (every 4 weeks) preparations of antipsychotic medications used in the maintenance treatment of individuals with schizophrenia and other psychotic disorders. Their use is often advocated for people at high risk of relapse or who are not fully adherent to oral medication regimens. There is a substantial difference in the costs for a year's treatment with these agents. However, no head-to-head comparison of these agents had been undertaken prior to ACLAIMS. In ACLAIMS, 311 individuals diagnosed with schizophrenia or schizoaffective disorder who were expected to

benefit from treatment with a long-acting injected antipsychotic medication were randomly assigned to up to 2 years of treatment with either HD or PP. The primary outcome measure was time to efficacy failure, defined as need for psychiatric hospitalization, need for additional antipsychotic, or discontinuation of the study antipsychotic due to inadequate therapeutic effect. Detailed information about any potential relapse was sent to an independent Outcomes Adjudication Committee who made the final determination as to whether the event was or was not a relapse. The OAC reviewed all cases. Repeated assessments of psychopathology were obtained over the course of the trial. Repeated determinations of extrapyramidal side effects, weight and metabolic measures, and prolactin and prolactin-related side effects were obtained. Subject participation in the study ended in July 2013. The presentation at SIRS will be the first conference presentation of the primary results of the study, including comparisons of time to efficacy failure and of adverse effects including extrapyramidal side effects, weight, lipids, blood glucose, and prolactin.

Learning Objectives:

- Participants will be familiar with the comparative efficacy of haloperidol decanoate and paliperidone palmitate in terms of rates of relapse, time to relapse, and PANSS scores.
- Participants will be familiar with the comparative tolerability of haloperidol decanoate and paliperidone palmitate in terms of weight, measures of lipid and glucose metabolism, prolactin, and extrapyramidal side effects.

Literature References:

- Rosenheck reference that is included in my submission.
- Covell NH, McEvoy JP, Schooler NR, Stroup TS, Jackson C, Rojas I, Essock SM. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres. J Clin Psychiatry 2012: 73;660-675.

PANEL
1:00 PM – 2:30 PM

PANEL OVERVIEW:
NIMH/NCCAM PANEL: CONDUCTING PRAGMATIC TRIALS IN MENTAL HEALTH: LESSONS LEARNED FROM THE NIH HEALTH CARE SYSTEMS RESEARCH COLLABORATORY

Emmeline Edwards[1], Wendy Weber[1], Greg Simon[2], Liz Delong[3]
[1]NIH, National Center for Complementary and Alternative Medicine (NCCAM), [2]Group Health Research Institute, [3]Duke University Medical Center

In the last few years there has been a growing interest in clinical trials testing research hypotheses which will directly inform health care systems. This interest has been driven by a number of factors including the high cost of traditional efficacy studies and the exclusion of many individuals from efficacy trials leading to results that do not generalize to large patient populations. Pragmatic and comparative effectiveness research designs can be applied to mental health research to answer clinical research hypotheses that will have a direct impact on policy and practice. The NIH Health Care Systems Research Collaboratory has funded the planning of seven pragmatic trials, including a suicide prevention intervention study. Lessons learned during the planning of these pragmatic trials will be presented to assist the scientific community overcome potential barriers they may encounter when planning pragmatic trials. Presenters will

highlight examples of key elements of study design that must be addressed prior to launching pragmatic trials including: effective integration of intervention delivery into the health care system; how to select the appropriate randomization level (patient, doctor, clinic, unit, or hospital) for cluster randomization designs; data quality in electronic health records; and issues related to consent and ethical oversight of interventions that are already provided in standard health care. In addition, NCCAM staff will also provide an overview of funding opportunities and priorities for pragmatic and CER studies available at NIH. The symposium presentations will highlight the potential of applying the methods and models of pragmatic trials to the field of mental health research and the challenges that need to be considered: 1) Dr. Wendy Weber (National Center for Complementary and Alternative Medicine -NCCAM/NIH) will provide a brief introduction to pragmatic trials and an overview of the Health Care Systems Research Collaboratory activities during the planning and implementation of a series of pragmatic trials. Dr. Weber participates in the ethics and regulatory work group of the collaboratory, so she will discuss some of ethical and regulatory issues that presented challenges in the pragmatic trials. She will also discuss ongoing NIH research collecting empirical data on patient and IRB perspectives on the ethical issues of conducting research on interventions that are already part of standard care. Finally, she will provide an overview of funding opportunities available at NIH for pragmatic and CER studies; 2) Dr. Greg Simon (Group Health Research Institute) will describe the planning activities of his pragmatic trial assessing two online selective suicide prevention programs. Challenges addressed in the planning of this trial included verification of event rates and estimation of eligible patients; uptake of the online interventions; and ethical oversight issues considered when determining when consent is needed for such a study; 3) Dr. Liz Delong (Duke University) will focus her presentation on the statistical considerations that are specific to pragmatic trials and the innovative randomization methods used in the projects of the HCS Collaboratory.

Learning Objectives:

- Attendees will leave the symposium with a better understanding of the challenges that must be addressed prior to conducting pragmatic and comparative effectiveness research study designs.
- Attendees will also learn several innovative design and practical recommendations for overcoming potential barriers.

INDIVIDUAL RESEARCH REPORTS
3:30 PM – 4:30 PM

ANXIETY DISORDER PRESENTATIONS

INDIVIDUAL ABSTRACT:
A RAPIDLY ACTING INTRANASAL TREATMENT FOR THE SYMPTOMS OF GAD
Michael R. Liebowitz[1], Louis Monti[1], Rita Hanover[2], Bernard Grosser[3]
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Although Generalized Anxiety Disorder (GAD) is a common and sometimes disabling condition, there is a need for additional treatments other than benzodiazepines that can be used on a prn basis to help with the severe anxiety and distress that many affected individuals experience. PH94B is a new investigational drug for the acute treatment of Social Anxiety Disorder. Chemically, PH94B is an odorless, neuroactive steroid compound with proven lack of affinity to steroidal hormone receptors. It is thought to act via nasal chemosensory receptors that broadcast

chemosensory information to specific brain areas (cingulate gyrus, hypothalamus, limbic amygdala, anterior gyrus and prefrontal cortex) which are different from the brain areas activated by olfactory stimuli. Earlier studies demonstrated that picomol quantities of PH94B induced dose-dependent membrane currents and increased Ca2+ in isolated human nasal chemosensory cells, and depolarization of the human nasal chemosensory epithelium, followed by small but significant decreases in heart rate, respiratory rate, electrodermal activity, and blinking reflex, and increased alpha-EEG and body temperature. A number of the volunteers spontaneously reported feeling distinctly calm and less nervous during these studies. Similar results were obtained in a Phase I dose escalation study. To continue this exploration of PH94B, 28 patients with GAD (DSM-IV) were enrolled in a randomized, placebo-controlled, double blind study. Following exclusion of placebo responders (n = 7) 21 patients were randomized to receive 200 pg PH94B or placebo in a one second aerosol pulse to the chemosensory epithelium of the anterior nasal septum. HAM-A, and clinical electrophysiological measures were administered at randomization (Baseline) and 30 and 60 min following treatment. Because of the small sample size and lack of power, effect sizes (Cohen's d) were evaluated in addition to between-group comparisons. Nineteen completed the study (2 early terminators). Thirty minutes after treatment there was mean reduction of 32.0% (8.7 points) for the PH94B group (n = 11) and 19.6% (5.1 points)for the Placebo group (n = 8) in total HAM-A (p = 0.09, one-tail t-test; Cohen's d = 0.644). Electrophysiological changes (respiratory, cardiac, and electrodermal frequency), concordant with the reduction in anxiety, were significantly greater for the PH94B group (p's < 0.003, one-tail; Cohen's d range: 1.3 to 8.0). Further exploration of group differences for individual HAM-A item scores revealed impressive effect sizes for improvement in Anxious Mood Cognition Depressed Mood Cardiovascular Symptoms and Other Autonomic Symptoms (Cohen's d range: from 0.469 to 1.59). After 60 min, all significant improvements and group differences had disappeared. PH94B may be useful as a prn treatment for GAD, although further trials with larger samples are indicated. PH94B may be useful in other anxiety states where rapid, temporary relief would be of benefit, like performance and social anxiety that is part of social anxiety disorder. In fact, this was recently demonstrated in a placebo controlled trial. Nasal chemosensory cells may be a portal of entry for substances affecting feeling states.

Learning Objectives:

- To highlight the need for treatments that can be used on a prn basis to help with severe anxiety and distress.
- To describe ongoing research in the development of a novel, putative prn treatment for anxiety disorders.

INDIVIDUAL ABSTRACT:

COMPARATIVE EFFECTIVENESS OF PROLONGED EXPOSURE (PE) AND SERTRALINE(SER) IN PTSD:FINAL ANALYSES OF THE IMPACT OF CHOICE AND TREATMENT PREFERENCE ON ACUTE OUTCOME.

Matig Mavissakalian[1], Norah Feeny[2], Lori Zoellner[3], Peter Roy-Byrne[4]

[1]Case Western Reserve University School of Medicine, [2]Case Western Reserve University, [3]University of Washington, [4]University of Washington School of Medicine

There are no large scale clinical trials directly comparing prolonged exposure (PE) and SSRIs in posttraumatic stress disorder (PTSD). Furthermore, these evidence based treatments are radically different with PE patients are encouraged to directly approach the trauma memory and trauma-related fears while with pharmacotherapy, such as sertraline (SER), this level of engagement

with the trauma-related stimuli is not necessary. The present NIMH funded study used a doubly-randomized preference trial design to examine and compare treatment choice and outcome between PE and SER in 200 subjects with chronic PTSD. Prior to randomization, participants viewed detailed, counterbalanced videotaped treatment rationales of both PE and SER. After viewing these rationales, participants were asked for their treatment preference. Then, they were first randomized to choice or no choice treatment and those in the no choice arm were randomly assigned to either PE or SER. Treatments in choice or no choice arms were similar and consisted of 10 weeks of PE or SER when responder status was determined by independent/blind assessors with planned follow-up assessments at 3,6,12 and 24 months. The majority (61%) of participants preferred PE ($p<.01$). Both prolonged exposure and sertraline showed relatively medium to large pre- to post effect sizes in reducing PTSD and secondary outcome measures of depression and anxiety with approximately 50 % clinically marked significant response rates . Further, treatment preferences were strongly associated with both patient dropout and worse treatment adherence ($p<.0005$). Sensitivity analyses used propensity scores to adjust for characteristics associated with preference for treatment, as well as EM algorithm multiple imputation of five datasets to examine whether these factors influenced findings. The overall patterns remained the same. If people completed treatment, they had similarly good outcomes regardless of treatment preference, but participants were likely to drop out prematurely if their treatment choice and assignment were discrepant. In conclusion, results showed comparable effectiveness between PE and SER and a significant effect of patient choice or treatment preference on better treatment adherence/completion mediated outcome. Clinical implications will be discussed highlighting the importance of patient preferences that question one-size fits all approaches to treatment for patients suffering from PTSD.

Learning Objectives:

- To appreciate the comparative effectiveness of two radically different evidence based treatments for PTSD.
- To appreciate the importance and impact of choice and receiving one's preferred treatment on the short term outcome of PE and Sertraline in PTSD.

INDIVIDUAL ABSTRACT:

PHARMACOGENETIC STUDY OF GENETIC VARIATIONS ACROSS REMOTE REGULATORY REGIONS OF 14 OBSESSIVE-COMPULSIVE DISORDER CANDIDATE GENES IN ANTIDEPRESSANT RESPONSE

Gwyneth Zai[1], Clement Zai[2], Vanessa Goncalves[2], James Kennedy[3], Margaret Richter[4]
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Obsessive-compulsive disorder (OCD) is a chronic and debilitating disorder with a strong genetic etiology. Genetic associations between OCD and several candidate genes including the glutamate transporter (SLC1A1), monoamine oxidase (MAOA), glutamate NMDA receptor 2B (GRIN2B), serotonin 2A receptor (5HTR2A), serotonin transporter (SLC6A4), brain-derived neurotrophic factor (BDNF), and catecholamine-O-methyl transferase (COMT) genes have previously been reported. Pharmacogenetics represents a valuable alternative strategy to define subtypes of OCD and to define clinically useful inter-individual genetic variation in drug response. We investigated 14 genes including those mentioned above as well as top hit genes

from a recent OCD genome-wide association study: Disks Large (drosophila) homolog-associated protein 1 (DLGAP1), BTB (POZ) domain containing 3 (BTBD3), serotonin 1B receptor (5HT1B), SLIT and NTRK-like family (SLITRK5), Fas apoptotic inhibitory molecule 2 (FAIM2), glutamate receptor, ionotropic, kainite 2 (GRIK2), and fucosyl-transferase 2 (FUT2). We examined a total of 32 single nucleotide polymorphisms across these candidate genes and their regulatory regions using a custom-made 32-SNP OpenArray® chip and genotyping was performed using the QuantStudioTM 12K Flex Real-Time PCR System in 222 OCD patients with retrospective response data on multiple serotonin reuptake inhibitor (SRI) trials. Individuals were grouped into those who improved following an adequate trial of one or more SRI(s) as compared with those who reported "minimal", "no change", or "worsening". Genotypes and response data were examined on a combined SSRI/SRI basis. Interesting associations ($P<0.05$) were detected for DLGAP1, SLITRK5, BTBD3, 5HT1B, and SLC1A1 in SSRI/SRI response. These results suggest that genetic variants may play a role in SRI response to OCD. Combination of these variants may be clinically useful in predicting treatment resistance versus response in OCD.

Learning Objectives:

- To recognize the importance of genetic variations in antidepressant response in OCD patients.
- To develop an understanding in remote regulatory regions in the genetics of antidepressant response in OCD.

INDIVIDUAL ABSTRACT:
EMOTION RECOGNITION DEFICITS IN TREATED AND UNTREATED ADULTS WITH ADHD

Anneka Tomlinson[1], Joanna C. Neill[1], Joe Johnson[2], Robert Baskind[3]
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Introduction: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder now known to persist into adulthood. ADHD comprises of clusters of symptoms of inattention, impulsivity and hyperactivity. In adulthood ADHD presents a different profile compared with children, with fewer externalizing symptoms and higher rates of comorbidity. Both children and adults with ADHD have documented higher rates of impairments with regards to interpersonal and social functioning compared to those without ADHD. Deficits in emotion recognition during childhood have been proposed to underpin the social malfunctioning in ADHD. To date little is known about nonverbal emotion recognition in adults with ADHD, and in particular with respect to the subtypes of ADHD. Aims: 1. To compare the emotion recognition abilities in treated and untreated adults with ADHD and healthy controls. 2. To compare the emotion recognition abilities between the different subtypes of ADHD. Methods: Participants were recruited from two specialist National Health Service adult ADHD clinics in England. The sample consisted of 105 participants (men=66, women=49) divided into three groups: ADHD treated (ADHD-T; n=39), ADHD untreated (ADHD-UnT; n=42), and healthy controls (n= 24). The mean age was 29 years. All participants diagnosed with ADHD must have met the criteria outlined in DSM-IV. All ADHD participants completed a full self-report Connors Adult ADHD Rating Scale, WEISS-Global Impairment Rating Scale and five neurocognitive tasks using the Cambridge Automated Neuropsychological Test Battery (CANTAB). The Emotion Recognition Task (ERT) – CANTAB task, was used to assess emotion recognition. ERT measures the ability to identify emotions in facial expressions. The participant was shown a series of faces, which appear on the

screen briefly and were asked to identify the emotion (happiness, sadness, anger, disgust, surprise and fear). Computer-morphed images were derived from the facial features of real individuals each showing a specific emotion, are displayed on the screen. Results: ANOVA revealed that the ADHD-UnT group made more errors when presented with faces displaying fear, disgust and anger; relative to healthy controls ($p<0.001$). ANOVA also revealed that the ADHD-UnT group made more errors when presented with faces displaying disgust and anger, relative to ADHD-T ($p<0.001$). Finally, ADHD-T group made more errors when presented with faces displaying fear, disgust and anger, relative to healthy controls ($p<0.001$). Discussion: We have shown that adults with ADHD have impairments in facial emotion recognition in comparison to healthy controls. This study also provides evidence that standard ADHD medication (methylphenidate and/or atomoxetine), improves emotion recognition, specifically anger and disgust recognition. These findings highlight the importance of focusing on social cognition as a target for treatment and the importance of social functioning on the level of impairments in daily life of adults with ADHD. Future directions: We are still analyzing data with respect to ADHD subtype differences, with the hypothesis to observe differences in correct responses in respect to three emotions: fear, disgust, anger.

Learning Objectives:

- To widen the understanding and acceptance of ADHD as a valid, impairing psychiatric condition in adulthood.
- Improve the understanding of the neurocognitive deficits associated with adult ADHD and the subtypes of adult ADHD, with a specific focus on emotion recognition. Including, highlighting the differential effects of the stimulant drugs and non-stimulant drugs on various aspects of cognition and symptomatology.

DEPRESSION PRESENTATIONS

INDIVIDUAL ABSTRACT:
THE EFFICACY OF VORTIOXETINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND HIGH LEVELS OF ANXIETY SYMPTOMS: A META-ANALYSIS

David Baldwin[1], François Ménard[2], Henrik Loft[2], Yinzhong Chen[3], Atul R. Mahableshwarkar[4]
[1]University of Southampton, [2]H. Lundbeck A/S, [3]Takeda Development Center Americas, Inc, [4]Takeda Development Center Americas Inc.

Background: Vortioxetine 5–20 mg/day was approved by the FDA in September 2013 and by the European Commission in December 2013 for treatment of major depressive disorder (MDD) in adults. With direct modulation of receptor activity and inhibition of the serotonin transporter, in vitro studies have shown vortioxetine to have a multimodal mechanism of action.1,2 Objective: To evaluate the clinical effect of vortioxetine compared with placebo in MDD patients with high levels of anxiety. Methods: A random-effects meta-analysis was conducted on data from 9 randomized, placebo-controlled clinical trials of vortioxetine (5–20 mg/day) in adults with MDD (full analysis set, mixed model for repeated measures analysis). Additional tests were conducted for heterogeneity. All patients met DSM-IV criteria for a Major Depressive Episode and had a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score of >22 (1 study), >26, or >30 (2 studies). Results were stratified by baseline Hamilton Anxiety Scale (HAM-A) score (score ≥20 defined high level of anxiety symptoms). The principal outcome was the difference in change from baseline (CFB) to study end (week 6/8) in MADRS total score (TS) for vortioxetine vs placebo. Additional outcomes included change from baseline in HAM-A score. Results: Of

2416 patients treated with vortioxetine, 1210 (50.1%) had a baseline HAM-A score ≥20. Vortioxetine showed a dose response on the MADRS TS in the high HAM-A patient subgroup, with a mean difference from placebo in CFB of –3.3 (5 mg, n=361; P<0.001), –3.8 (10 mg, n=315; P<0.001), –1.1 (15 mg, n=171; P=NS), and –5.1 points (20 mg, n=156; P<0.005). These findings are similar to the effect of vortioxetine vs placebo on MADRS TS at week 6/8 in the total MDD population: –2.6 (5 mg, n=714; P<0.01), –3.5 (10 mg, n=571; P<0.001), –2.6 (15 mg, n=344, P=NS), and –4.5 points (20 mg, n=359; P<0.001). Vortioxetine also reduced anxiety symptoms in patients with baseline HAM-A ≥20. For this subgroup of patients, vortioxetine showed a dose-related improvement, with a mean difference from placebo in at week 6/8 to week 6/8 in HAM-A of –2.0 (5 mg; P<0.01), –2.1 (10 mg; P<0.01), –0.2 (15 mg; P=NS), and –2.4 points (20 mg; P<0.1). This was similar to effects in the total MDD population, where the mean difference from placebo for vortioxetine in HAM-A score was –1.5 (5 mg; P<0.05), –1.7 (10 mg; P<0.05), –0.9 (15 mg; P=NS), and –2.0 points (20 mg; P<0.05). Conclusions: Highly anxious depressed patients are known to be more resistant to treatment than patients with a low level of anxiety; however, in this analysis in depressed patients with HAM-A score >20, vortioxetine demonstrated significant clinical improvements in depressive and anxious symptoms at 5, 10, and 20 mg doses. 1. Mørk A, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. J Pharmacol Exp Ther. 2012;340:666-675. 2. Adell A. Lu-AA21004, a multimodal serotonergic agent, for the potential treatment of depression and anxiety. Idrugs. [Review]. 201013:900-10.

Learning Objectives:

- To evaluate the efficacy of vortioxetine 5–20 mg/day on anxiety symptoms in adults with MDD.
- To evaluate the antidepressant efficacy of vortioxetine in adults with MDD and high anxiety levels.

INDIVIDUAL ABSTRACT:

ERYTHROPOIETIN INDUCES GROWTH IN LEFT HIPPOCAMPUS AND IMPROVES VERBAL MEMORY IN PATIENTS WITH SEVERE AFFECTIVE DISORDERS

Kamilla Woznica, Miskowiak

Psychiatric Center Copenhagen, Copenhagen University Hospital

Purpose Depression and bipolar disorder (BD) are associated with reduced neuroplasticity, reduction in hippocampal volume and memory impairment. Available drug treatments fail to reverse patients' cognitive impairments which persist into periods of remission and impede patients' functional recovery. Recent evidence suggests that erythropoietin (EPO) increases neuroplasticity and improves cognitive function in patients with treatment-resistant depression (TRD) (1) or bipolar disorder (BD) (2). The aim of this study was to investigate whether the cognitive improvement in these EPO-treated patients may be associated with structural changes in the hippocampus. Methodology Patients with TRD, who were moderately depressed (Hamilton Depression Rating Scale 17-items; HDRS-17 score > 17), or with BD in partial or full remission (HDRS and Young Mania Rating Scale; YMRS scores < 14) were randomized, with stratification by age and gender, to receive eight weekly EPO (Eprex; 40,000 IU) or saline (NaCl 0.9%) infusions in a double-blind, parallel-group design. Magnetic Resonance Imaging (MRI) and verbal memory assessments took place at baseline and at week 14, six weeks after treatment completion. Structural change in the hippocampus was examined using FMRIB's integrated registration and segmentation tool (FIRST), part of FSL (version 5.0.5). Total hippocampal

volume at each time was calculated in FSL and compared between groups using Statistical Package for the Social Sciences (SPSS, version 19 for IBM). Hippocampal shape change was analyzed using FSL vertex analysis. Results 84 patients were randomized to EPO (N=42) or saline (N=42). One patient withdrew at baseline, six patients did not complete follow-up scans, and data was lost for eight patients due to technical problems; Data for 70 patients was thus entered into the analysis. Change in total hippocampal volume showed no differences between groups (ANCOVA adjusted for age, gender and diagnosis: p-values>0.14). However, EPO increased growth in middle and posterior sub-regions of the left hippocampus in comparison with saline ($Z=3.0$, $P < 0.05$, cluster-corrected). EPO also enhanced verbal memory (ANCOVA adjusted for age, gender, diagnosis, and depression symptoms: $F(1,64)=4.15$, $P=0.05$). Multiple regression analysis with hippocampal growth, diagnosis, group, and depression symptoms as predictor variables revealed that memory improvement was solely predicted by hippocampal growth (model: $F(4,69)=2.50$, $P=0.05$; hippocampal growth: $Beta=0.28$, $P=0.03$; for the other variables: P-values>0.18). Importance EPO increased growth in the left hippocampus which predicted memory improvement. This may be a key neurobiological mechanism underlying memory improvement in EPO-treated patients with affective disorder. References (1) Miskowiak KW, Vinberg M, Christensen EM, Bukh JD, Harmer CJ, Ehrenreich H, Kessing LV: Recombinant human erythropoietin for treating treatment-resistant depression: A double-blind, randomized, placebo-controlled phase 2 trial. Neuropsychopharmacology 2013 (doi: 10.1038/npp.2013.335) (2) Miskowiak KW, Ehrenreich H, Christensen EM, Kessing LV, Vinberg M: Recombinant human erythropoietin to target cognitive dysfunction in bipolar disorder: A double-blind, randomized, placebo-controlled phase 2 trial (under review)

Learning Objectives:

- To meet and network with senior researchers in this field.
- To learn about key issues and caveats in conductance of psychiatric drug development research through the workshop led by experts from NIMH, NIDA, NIAAA, FDA, academia, and industry.

INDIVIDUAL ABSTRACT:

EPIDURAL CORTICAL STIMULATION OF THE LEFT DLPFC LEADS TO DOSE-DEPENDENT ENHANCEMENT OF WORKING MEMORY IN PATIENTS WITH MDD

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Background: Cognitive deficits are common across neuropsychiatric disorders, and a primary cause of functional disability. Nevertheless, clinicians have limited therapeutic options to facilitate cognitive enhancement, particularly of executive functions. We present results from a multicenter clinical trial of epidural cortical stimulation in patients with Major Depressive Disorder (MDD). The initial dose determination algorithm revealed acute dose-dependent facilitation of working memory function, suggesting specific therapeutic targets for device-based interventions. Methods: Ten patients with recurrent MDD without psychotic features were enrolled. Electrodes were surgically implanted in the left DLPFC. In order to determine the stimulation parameters, an algorithm was used to assess changes in working memory, mood and anxiety as a function of parametric variations in current amplitude. The Paced Visual Serial Addition Task was used to assess working memory, and Visual Analogue Scales for “Sadness” and “Anxiety”. Data were analyzed using repeated measures ANOVAs. Results: Patients tolerated the intervention well without significant side-effects. We observed a statistically significant relationship between current amplitude and working memory performance ($p=0.020$)

and reaction times (p=0.035): higher current led to improved performance and reduced reaction times. We observed a non-significant trend for "sadness" and "anxiety": higher current led to reduced scores for both. Conclusion: These data highlight the relevance of the left DLPFC as a therapeutic target for cognitive enhancement in neuropsychiatric populations. In addition, it confirms the capacity of brain stimulation to improve executive function in compromised patients. Similar strategies may be effective in other clinical populations with compromised cognition, possibly with noninvasive interventions.

Learning Objectives:

- Brain stimulation therapies can have a role in cognitive enhancement of compromised populations.
- Stimulating the left dorsolateral prefrontal cortex can improve executive function.

INDIVIDUAL ABSTRACT:

A PHASE 1B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-DOSE ESCALATION STUDY EVALUATING THE EFFECTS OF NSI-189 PHOSPHATE, A NEUROGENIC COMPOUND, IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD)

Maurizio Fava[1], Karl Johe[2], Lev Gertsik[3], Larry Ereshefsky[4], Bettina Hoeppner[5], Martina Flynn[6], David Mischoulon[7], Gustavo Kinrys[7], Marlene Freeman[8]

[1]Massaschusetts General Hospital Department of Psychiatry, [2]Neuralstem, Inc., [3]California Clinical Trials Medical Group, [4]PAREXEL International, [5]Harvard Medical School,, [6]Massachusetts General Hospital Clinical Trials Network and Institute, [7]Massachusetts General Hospital, Harvard Medical School, [8]Massachusetts General Hospital

NSI-189, a benzylpiperizine-aminiopyridine, is a novel chemical developed by Neuralstem Inc. for the treatment of major depressive disorder, based on preclinical evidence of neurogenesis in human hippocampus-derived neural stem cells in vitro and in mouse hippocampus in vivo. NSI-189 has also shown behavioral efficacy in the novelty suppressed feeding after daily oral administration for 28 days. This is an early phase, double-blind, randomized, placebo-controlled, multiple-dose study with three ascending cohorts. The first cohort received 40 mg QD, the second cohort 40 mg BID, and the third cohort 40 mg TID. 24 patients with major depressive disorder (MDD) were recruited, with their diagnosis and illness severity confirmed through an independent, remote SAFER interview from the MGH CTNI raters. Each cohort included at least 3 female subjects. Each patient underwent a Screening for eligibility (Day -37 to Day -6 or -3) and eligible patients were admitted into the unit on Day -5 to complete their wash-out and be reconfirmed for eligibility and for baseline assessments. Eligible patients receive daily dosing of investigational medicinal product (NSI-189 Phosphate or placebo) for 28 days starting on Day 1 and were followed for safety, PK, and PD until discharge. At the conclusion of in-house dosing (Day 28), patients remained in the unit for up to 3 additional days, at the psychiatrist's discretion. On Day 35 (± 3), Day 42 (± 3), Day 49 (± 3) and Day 70 (± 3) outpatient follow-up visits took place. Patients returned to the unit for extensive follow-up on Day 56 (± 3) and Day 84 (± 3) (End-of-study). The efficacy assessments included the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinician Global Impression – Improvement (CGI-I), the Symptoms of Depression Questionnaire (SDQ) and the Cognitive and Physical Functioning Questionnaire (CPFQ). Despite the minimal improvement observed among the placebo-treated patients, at day 28, the efficacy measurements showed a clinically meaningful reduction in depressive and cognitive symptoms across all measures for the two lower doses (40 mg/day and 80 mg/day) but

not for the highest dose (120 mg/day). These improvements appeared to persist over time during the follow-up for MADRS, SDQ, and CPFQ. In terms of safety, no serious AEs occurred and the drug was well tolerated. The main limitations of this study are the relatively small sample size of each cohort and the fact that efficacy analyses were not the primary aim, and were meant to be only descriptive in nature. In summary, a novel neurogenic compound, NSI-189, has shown promise as a potential treatment for MDD in a Phase 1B, double-blind, randomized, placebo-controlled, multiple-dose study with three ascending cohorts. These preliminary findings support the view that a neurogenesis-based platform can identify promising new treatments for MDD (Fava et al, 2012). The possible inverted U dose-response curve observed in this study is consistent with previously reported inverted U dose-response curve of compounds enhancing synaptic plasticity (Lavergne and Jay, 2010). Further studies are necessary to confirm these preliminary observations.

Learning Objectives:

- To learn about the potential usefulness of novel neurogenic compounds in depression.
- To learn about the safety and efficacy of NS189 in the treatment of depression.

SCHIZOPHRENIA AND BIPOLAR DISORDER PRESENTATIONS

INDIVIDUAL ABSTRACT:
CAN OXYTOCIN ENHANCE LEARNING DURING SOCIAL COGNITIVE SKILLS TRAINING IN SCHIZOPHRENIA?

Michael C. Davis[1], Michael F. Green[2], Junghee Lee[3], William Horan, Jonathan K. Wynn[4], Stephen R. Marder[5]
[1]VA Greater Los Angeles; University of California Los Angeles, [2]UCLA Semel Institute for Neuroscience and Human Behavior, [3]UCLA, [4]VA Greater Los Angeles Healthcare System/UCLA, [5]Semel Institute at UCLA and VISN 22 MIRECC

Background: Impairments in social cognition are common in schizophrenia and predict poor functional outcome. This proof-of-concept study assessed whether intranasal oxytocin (OT), given prior to social cognitive training sessions, enhances learning of social cognitive skills. Methods: 27 male schizophrenia outpatients schizophrenia participated in 6-weeks (12-sessions) of social cognitive skills training groups. Training focused on three domains: facial affect recognition, social perception, and empathy. Subjects were randomly assigned to receive intranasal OT or placebo 30 minutes prior to each session. Participants did not receive OT between sessions or on the day of assessments. We evaluated scores on social cognition tests in the three domains, as well as clinical symptoms and neurocognition, at baseline, one week post-training, and one month later. Results: Subjects receiving OT demonstrated significantly greater improvements on an empathic accuracy test than those receiving placebo at post-training ($p=.03$, Cohen's $d=.92$) and one month follow-up ($p=.03$, $d=.98$). There were no OT-related effects for the other social cognitive tests, clinical symptoms, or neurocognition. There were main overall effects of time (indicating improvement) on facial affect recognition and social perception tests. Conclusions: This study provides initial support for the idea that OT can enhance learning during social cognitive training sessions. The effects were most pronounced on empathic accuracy, a high-level social cognitive process that has been challenging to improve through existing social cognitive remediation programs. Combining pharamacological and psychosocial is a promising approach to helping patients to acquire social cognitive skills needed to improve daily functioning in the community.

Learning Objectives:

- Assess whether administering intranasal oxytocin prior to social cognitive skills training can enhance learning.
- Assess feasibility and tolerability of study protocol.

INDIVIDUAL ABSTRACT:

HOSPITALIZATION RATES IN PATEINTS SWITCHED FROM ORAL ANTIPSYCHOTICS TO ARIPIPRAZOLE ONCE-MONTHLY: A MIRROR STUDY

John Kane[1], Cathy Zhao[2], Brian R. Johnson[3], Ross A. Baker[3], Anna Eramo[4], Robert D. McQuade[3], Anna R. Duca[5], Timothy Peters-Strickland[3]

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Objective: Assess hospitalization rates in patients with schizophrenia treated prospectively with aripiprazole once-monthly 400 mg (AOM-400; an extended-release injectable suspension with efficacy in the treatment of schizophrenia[1]) compared with the same patients previously treated with oral antipsychotics. Methods: A multicenter, open-label study in stable patients with schizophrenia treated prospectively (6 months) with AOM-400 compared with a retrospective treatment (6 months) with oral antipsychotics in a naturalistic community setting. Eligible patients were aged 18–65 years with a current diagnosis of schizophrenia (DSM-IV-TR criteria), a history of illness (>1 year), and 7 months of hospitalization data. The prospective treatment arm had two phases: a conversion phase (Phase A; 4 weeks) where patients were cross-titrated to oral aripiprazole (ARI) monotherapy; and a 24-week, open-label treatment phase (Phase B) where patients received AOM-400 (option to decrease to 300 mg), while receiving concomitant ARI for the first 14 days from the start of Phase B. The primary endpoint was to compare psychiatric hospitalization rates (proportion of patients with ≥1 inpatient psychiatric hospitalization) between oral antipsychotic treatment (retrospective analysis, months -4 to -1 prior to oral conversion) and after switching to AOM-400 (prospective analysis, last 3 months [i.e. month 4 to 6 after AOM-400 initiation]). Safety and tolerability were also assessed. Results: Of 433 subjects in the efficacy analysis, 336 entered the 4th month of Phase B and were part of the primary efficacy outcome comparison: hospitalization rates for patients receiving AOM-400 (2.7% [n=9/336]) were significantly lower than for the same patients previously treated with oral antipsychotics (27.1% [n=91/336]; p<0.0001). All-cause discontinuations during the entire prospective phase B were 32.3% (n=140/433). The most common reasons for discontinuation were: patient withdrew consent, 9.5% (n=41/433); adverse events, 8.5% (n=37/433); and patient lost to follow-up, 7.6% (n=33/433). Adverse events with >=5% incidence were insomnia 6.7% (n=29/431), and akathisia 6.5% (n=28/431). Conclusions: Switching to aripiprazole once-monthly from oral antipsychotics produced a significant and marked improvement in rates of psychiatric hospitalizations, confirming results from a preliminary analysis[2] of a subset of patients. References 1 Kane JM, Sanchez R, Perry P, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week multicenter, randomized, double-blind, placebo-controlled study. J Clin Psych. 2012;73(5):617–624. 2Kane JM, Sanchez R, Zhao J, et al. Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly for the management of schizophrenia. J Med Econ. 2013 Jul;16(7):917-25.

Learning Objectives:

- Understand the design of a 6-month mirror study assessing hospitalization rates between patients treated prospectively with aripiprazole once-monthly and retrospectively with oral antipsychotics.
- Recognize the efficacy and safety of aripiprazole once-monthly in a naturalistic study.

INDIVIDUAL ABSTRACT:
LITHIUM ENHANCES MITOCHONDRIAL COMPLEX I ACTIVITY AND AMELIORATES DNA METHYLATION AND HYDROXYMETHYLATION INDUCED BY MITOCHONDRIAL COMPLEX I DYSFUNCTION

Ana Cristina Andreazza, Gustavo Scola, Helena Kim, L. Trevor Young
University of Toronto

Mitochondrial complex I dysfunction is consistently reported in bipolar disorder (BD). Alterations in DNA methylation levels have also been reported in BD, and lithium was found to change DNA methylation profile in patients with BD. One of the mechanisms by which lithium may exert its effects in BD is by improving mitochondrial complex I function. Therefore, in order to examine whether complex I dysfunction induces methylation and hydroxymethylation of DNA, we treated rat primary cortical neurons with rotenone, which is an inhibitor of complex I, and evaluates the role of lithium in protecting this alterations. Rotenone was found to diminished complex I activity, which decreases ATP production and increase apoptotic cells. Moreover, complex I dysfunction increased levels of 5-methylcytosine (5mc) and hydroxymethylcytosine (5hmc), suggesting a possible association between complex I dysfunction and DNA alterations. Importantly, lithium was able to ameliorate rotenone-induced damage to mitochondrial complex I function, cell viability and prevent changes to DNA methylation and hydroxymethylation. These findings suggest that dysfunction of mitochondrial complex I increases global DNA methylation and hydroxymethylation in rat primary cortical neurons and demonstrated the ability of lithium to ameliorate such modifications. Future studies are needed to elucidate which specific genes are affected by mitochondrial complex I function, as well as, which ones are targeted by lithium. These may be important to understand epigenetic regulation in BD.

Learning Objectives:
- To understand whether mitochondrial complex I dysfunction can lead to changes in DNA mehtylation/hydroxymethylation levels.
- To understand the role of lithium in preventing alterations to DNA methilation/hydroxymethylation induced by mitochondrial complex I dysfunction.

INDIVIDUAL ABSTRACT:
VARENICLINE FOR SMOKING CESSATION IN BIPOLAR DISORDER: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Roy K.N. Chengappa
Western Psychiatric Institute and Clinic - University of Pittsburgh

Fifty years since the Surgeon General's Report on Tobacco and its harms (1964), smoking rates in the general population of the United States has declined from nearly 45 percent to just fewer than 20 percent with virtually no change in those diagnosed with mental illness. Nearly 1 out of 2 cigarettes in the United States is smoked by people with mental illness. Moreover, persons with schizophrenia or bipolar disorders are among the most addicted smokers and the least likely to quit but yet are excluded from most pre-approval smoking cessation studies. A few randomized clinical trials for smoking cessation have been completed in schizophrenia but virtually none in

bipolar disorder. Varenicline, a nicotine receptor partial agonist was tested in a randomized, placebo-controlled trial for smoking cessation in stable bipolar patients motivated to quit smoking. Sixty consenting men and women with Bipolar Disorder whose medications and mental state were stable were randomized to standard titration of varenicline (or placebo) for a 3-month treatment period and 3-months follow-up. Patients picked a target quit date, and were monitored weekly for psychopathology (YMRS, MADRS, and CGI), suicidal behavior (CSSRS) and side-effects. Smoking cessation counselling was provided to all. At each visit, in addition to self-report of smoking cessation (time-line follow back), biochemical verification in expired air was undertaken with a CO meter. Patients had to meet dual criteria to be considered abstinent, i.e. self-report and CO < 10 ppm, the primary outcome criterion. At 3-months (end of treatment), significantly more patients quit with varenicline (15/31, 48.4%) than with placebo (3/29, 10.3%), OR = 9.1 (95% CI, 2.03, 32.5), p = 0.002. By 6-months, several subjects had relapsed following the end of treatment, and the abstinence rates were 6/31 (19.4%) for varenicline-treated subjects vs. 2/29 (6.9%) for placebo-assigned subjects, OR = 3.2 (95% CI, 0.60, 17.6), p = 0.17. Psychopathology ratings remained stable under both treatment conditions. Ten serious adverse events occurred, n = 6 for varenicline and n = 4 for placebo. Abnormal dreams occurred more often in varenicline-treated patients (18/31, 61.3%) than those assigned to placebo (9/29, 31%), Fishers exact p = 0.04. Eight varenicline treated and five placebo assigned subjects expressed fleeting suicidal ideation. Depressed mood occurred more often in varenicline-treated subjects (8/31, 22.6%) than those assigned to placebo (2/29, 6.9%), Fishers exact p = 0.08. Varenicline shows efficacy for initiating smoking cessation in stable bipolar patients motivated to quit but trials of longer duration are warranted to maintain abstinence. Vigilance for neuropsychiatric adverse events is prudent when varenicline is being considered for smoking cessation in this patient population. Schroeder S, Morris C. Confronting a Neglected Epidemic: Tobacco Cessation for Persons with Mental Illnesses and Substance Abuse Problems. Annual Review of Public Health 2010; 31: 297-314. Cook B, Wayne G, Kafali E, Liu Z, Shu C, Flores M. Trends in Smoking Among Adults With Mental Illness and Association Between Mental Health Treatment and Smoking Cessation. JAMA. 2014; 311:172-182.

Learning Objectives:

- Participants will review the few studies of smoking cessation done in bipolar disorder.
- Appraise the results of a randomized clinical trial with varenicline to aid smoking cessation in bipolar disorder.
- Consider how these data may apply to practice or future research.

STATISTICAL METHODS, PERSONALITY DISORDERS, SUBSTANCE ABUSE, AND COMORBIDITY PRESENTAIONS

INDIVIDUAL ABSTRACT:
BRAIN-DERIVED NEUROTROPHIC FACTOR GENOTYPE AND AMYGDALA HABITUATION IN BORDERLINE PERSONALITY DISORDER

M. Mercedes Perez-Rodriguez[1], Antonia S. New[2], Qiaoping Yuan[3], Colin Hodgkinson[3], David Goldman[4], Larry Siever[1], Erin Hazlett[1]

[1]Mount Sinai School of Medicine, [2]James J Peters VAMC and Icahn School of Medicine at Mount Sinai, [3]National Institutes of Health, [4]NIAAA

Introduction: Borderline personality disorder is a psychiatric disorder characterized by emotion-processing abnormalities. Elucidating its underlying neural systems and genetic modulators and

fractionating it into neurobiologically defined pathophysiologic subtypes is crucial for refining testable models and developing personalized treatments for emotion dysregulation. Amygdala hyper-reactivity and deficient habituation are putative endophenotypes of abnormal emotion processing in BPD, which are under genetic modulation by brain-derived neurotrophic factor (BDNF) variants. The Met allele of the Val66Met SNP of the BDNF gene increases amygdala reactivity and impairs extinction learning, a phenomenon closely related to habituation. We aimed to use an imaging-genetics framework to examine for the first time in BPD patients the impact of BDNF Val66Met genotypes on amygdala habituation to repeated emotional and neutral pictures. We hypothesized that BDNF 66Met-carrying BPD patients would have a deficit in amygdala habituation to repeated unpleasant emotional pictures compared to non-Met carrying BPD patients and Met-carrying- and Non-Met carrying SPD and HCs. Methods: We employed event-related functional magnetic resonance imaging (fMRI) in 57 subjects (19 unmedicated BPD and 18 schizotypal personality disorder patients and 20 healthy controls) during a task involving viewing of unpleasant, neutral, and pleasant pictures, presented twice. We conducted an event-related BOLD response time-series analysis based on the amygdala region of interest, which was hand-traced on structural MRI for each individual participant and co-registered to the BOLD images. Amygdala responses were examined with a mixed-model multivariate MANOVA including BDNF Val66Met SNP genotype (Met-carriers vs. Non-Met carriers). Results: A significant Diagnostic group×Genotype (BDNF Val66Met SNP Met- vs. Non-Met-carriers)×Picture type (unpleasant, neutral, pleasant)×Picture repetition (Novel/Repeat)×Time interaction indicated that Met-carrying BPD patients (but not Met-carrying SPD patients or HCs) showed exaggerated amygdala reactivity to repeated, but not novel, unpleasant pictures, representing a habituation deficit. Conclusions: This imaging-genetics study advances our knowledge of the neurobiology of emotional processing in BPD, by demonstrating for the first time that the deficit in amygdala habituation to emotional stimuli reported in BPD is modulated by the BDNF gene Val66Met polymorphism. This finding is important because it points to BDNF modulators as a novel therapeutic avenue for BPD, a disorder which lacks FDA-approved medications. References: Autry, A. E.. (2012). Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev, 64(2), 238-258. Hazlett, E. A. (2012). Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. Biol Psychiatry, 72(6), 448-456. Bath, K. G. (2006). Variant BDNF (Val66Met) impact on brain structure and function. Cogn Affect Behav Neurosci, 6(1), 79-85.

Learning Objectives:

- At the end of this presentation, attendees will familiar with the main neurobiological models of emotional processing in borderline personality disorder.
- At the end of this presentation, attendees will be familiar with the role of brain-derived neurotrophic factor (BDNF) variants in the modulation of amygdala responses to emotional stimuli.

INDIVIDUAL ABSTRACT:

ANALYSIS AND MISSING DATA HANDLING IN PSYCHIATRY TRIALS WITH INEVITABLE, HIGH, DIFFERENTIAL AND INFORMATIVE DISCONTINUATIONS

Yangchun Du, Asli Memisoglu, Marc de Somer, Robert Risinger, Bernard L. Silverman, Srdjan R. Stankovic, Elliot Ehrich
Alkermes, Inc.

Background: High, differential (by treatment arm) and informative (missing-not-at-random, MNAR) missing data are common in trials of psychiatric conditions with debilitating morbidity and disability. . This presents challenges for valid inference and estimation to clinicians, statisticians and regulators, especially in confirmatory trials. The National Research Council report on prevention and treatment of missing data in clinical trials generally recommends the use of direct likelihood, e.g., mixed models for repeated measurements (MMRM). The objective of the present research is to evaluate performance of direct likelihood and alternative methods, in the presence of high (≥40%), differential and informative missing data, for the design of a confirmatory trial in acute schizophrenia exacerbation. Methods: Simulation was used to generate and analyze data based on the continuous Positive and Negative Syndrome Scale (PANSS) score, with various patterns of missing data and across wide ranges of treatment effect, variability and sample size. Historic PANSS data informed simulation assumptions. Statistical analysis models and missing data handling options included MMRM, ANCOVA.LOCF, and methods based on discontinuation patterns. Performance metrics included type I error control, accuracy, precision and power versus sample size. Results: When missing data rates were below 40%, and discontinuations were non-differential and non-informative, MMRM controlled type I error and produced minimally biased estimates of effect, with optimal power. However, when missing data exceeded 40%, and became differential and informative, MMRM analysis resulted in inflated type I error and significant bias. The magnitude of bias depended on the proportion of informative missingness. Under these conditions, ANCOVA.LOCF proved more robust with higher accuracy, precision and tighter type I error control. Stratification and modeling by discontinuation reason and timing provided further insight. Discussion: The appropriate choice of a primary analysis and missing data handling method is crucial for the design and evaluation of confirmatory trials. ANCOVA.LOCF provided more robust inference compared to MMRM, under assumptions typical of clinical trials with high (≥40%), differential and informative missing data. Alternative analysis models and informative missing data handling methods, e.g., pattern mixture or selection models, add insight as part of sensitivity analyses. The findings suggest there is no single optimal analysis model and missing data handling method under all scenarios of discontinuation: the choice of method is best informed by simulation under assumptions relevant to the specific study context. In addition to the primary analysis, a broad set of sensitivity analyses will provide information on the robustness of the results. Literature references: Little RJ, D'Agostino R, Cohen ML et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012; 367(14): 1355-60

Learning Objectives:

- To understand the performance and optimal choice of analysis models and missing data handling options in clinical trials with high, informative and differential missing data.
- To identify opportunities for application and research of this method.

INDIVIDUAL ABSTRACT:

LONG-TERM SKELETAL EFFECTS OF RISPERIDONE AND SSRIS IN YOUTHS

Chadi Calarge, Trudy Burns, Janet Schlechte
University of Iowa

Background: In a previous cross-sectional study, we found lower bone mass during treatment with risperidone and selective serotonin reuptake inhibitors (SSRIs). Here, we evaluate the skeletal effects of these psychotropics at follow-up. Methods: Medically healthy 7 to 17 year-old males treated with risperidone for six months or more were enrolled and returned for follow-up,

1.5 years later. Treatment history was extracted from the medical and pharmacy records. Anthropometric, laboratory, and bone mass measurements (using dual x-ray absorptiometry [DXA] at the lumbar spine and peripheral quantitative computed tomography [pQCT] at the distal radius) were obtained at each research visit. Multivariable linear regression analyses compared participants who remained on risperidone at follow-up to those who had discontinued SGA treatment well as those who had received SSRIs versus not. Results: The sample consisted of 94 boys with a mean age of 11.8±2.7 years at study entry. The majority had an externalizing disorder and had received risperidone and SSRIs for 2.5±1.7 years and 1.6±1.9 years, respectively, by study entry. By follow-up, 26% (n=24) had discontinued risperidone. Compared to discontinuing risperidone, continuing it was associated with a significant decline in DXA-based age-sex-height-race-specific areal bone mineral density (BMD) z score at the lumbar spine and a significant failure to increase pQCT trabecular volumetric BMD at the radius, after accounting for significant covariates. In addition, taking an SSRI was associated with significantly reduced lumbar spine areal BMD z score and radius trabecular volumetric BMD at both study entry and follow-up but without further decline observed between the two visits. The use of SSRIs was associated with a trend for lower concentrations of osteocalcin, a marker of bone formation. Conclusions: To our knowledge, this is the first study to prospectively assess the skeletal effects of psychotropics. Chronic SSRI treatment in children and adolescents was associated with reduced, albeit stable, bone mass for age while chronic risperidone treatment was associated with failure to accrue bone mass. Literature References: 1- Calarge CA, Nicol G, Schlechte JA and Burns TL. Cardiometabolic Outcomes in Children and Adolescents Following Discontinuation of Long-term Risperidone Treatment. Journal of child and adolescent psychopharmacology, In Press. 2- Calarge CA, Zimmerman B, Xie D, Kuperman S and Schlechte JA. A cross-sectional evaluation of the effect of risperidone and selective serotonin reuptake inhibitors on bone mineral density in boys. J Clin Psychiatry 71:338-347, 2010.

Learning Objectives:

- To review the value of using DXA vs. pQCT to measure bone mass.
- To discuss the skeletal effects of extended use of risperidone and SSRIs in youths.

INDIVIDUAL ABSTRACT:
IMPULSIVITY AND SUBSTANCE DEPENDENCE: META-ANALYSIS AND POSSIBLE ROLE IN TREATMENT

Saddichha Sahoo
NIMHANS

Background and Objectives: Impulsivity has been linked to the abuse of several drugs of abuse including alcohol, cocaine, and amphetamines. This study aimed to review and quantitatively summarize standardized assessments of impulsivity in studies on substance dependence, in order to propose possible treatment strategies. Methods: We used keywords impulsivity and substance to narrow down our search on MEDLINE, EMBASE, Psychinfo and Google Scholar to include those studies that had reported impulsivity scores using validated and reliable assessment measures. We searched all English language studies from 1990 to August 2012 with 56 reports meeting the inclusion criteria and were reviewed by three abstractors independently. We generated weighted mean differences (WMDs) from pooled data using RevManager 5.0 from Cochrane analysis. Results: The Barratt Impulsivity Scale (BIS-11) (most common), Dickman Impulsivity Inventory (DII), the Eysenck Impulsiveness Questionnaire (EI) and the UPPS Impulsive Behavior Scale have been commonly used. 33 studies were included and 23 excluded

due to incomplete data or lack of comparison group. A WMD of 10.21 was observed for all substances on the BIS-11, 2.4 on the EI- Impulsivity domain, 4.8 on the DII and 20.6 on the UPPS Scale. Conclusion: Impulsivity is significantly higher in substance dependent subjects than non-substance users. Motor and non-planning impulsivity are key domains which result in higher impulsivity scores. Targeting impulsivity with pharmacological agents may result in better outcomes for substance dependent clients. Limitations: Certain studies had to be excluded because of inadequate information.

Learning Objectives:

- Impulsivity is a risk factor for the development of substance use, independent of other contributory factors.
- Targeting impulsivity with pharmacological agents may result in better outcomes for substance dependent clients.

WORKSHOP
4:45 PM – 6:45 PM

WORKSHOP OVERVIEW:
COGNITIVE DEFICITS IN DEPRESSION: WHAT ARE THEY? ARE THEY INDEPENDENT DIMENSIONS? ARE THEY TARGETS FOR TREATMENT?

Steven D. Targum[1], Craig Nelson[2], Scott Mackin, Maurizio Fava[3], Dan V. Iosifescu[4], Tiffany Farchione[5]
[1]Clintara LLC, [2]UCSF, [3]Massaschusetts General Hospital Department of Psychiatry, [4]Icahn School of Medicine at Mount Sinai, [5]US Food and Drug Administration

Cognitive deficits are often present in patients experiencing acute major depressive disorder (MDD) and bipolar depression. Measurable cognitive deficits are found in 30-40% of mixed-age depressed adults and in 50-60% of older adults. These cognitive deficits can involve memory, language, executive function, attention, and processing speed. In some patients, some specific cognitive deficits persist as side effects and/or residual symptoms after effective antidepressant treatment and contribute to functional impairment despite the absence of mood symptoms. The co-mingling of cognitive symptoms with other depressive symptoms in depressed patients complicates determination of whether the cognitive symptoms are part of the depressive diathesis, are independent symptoms, or both. This workshop will address the following questions using data obtained from recent clinical trials and audience participation: What is the nature of the cognitive deficits frequently encountered in depressed patients? What are the methods used to assess cognition including both neuropsychological tests and subjective patient reports? Are clinician-administered neuropsychological tests and subjective patient-reported cognitive assessments related? Are certain cognitive deficits more closely associated with depressive disorder whereas others are relatively distinct and independent symptoms? Is cognition a legitimate, distinct treatment target in patients with depressive disorder? Do different treatment modalities (including problem solving psychotherapy and antidepressant medications with different mechanisms of action) have different treatment effects on cognition and depressive symptoms? Dr. Mackin will review the nature and frequency of cognitive deficits in late life depression and methods used to assess these symptoms. He will present new data examining the relationship of the patient's perception of cognitive impairment with neuropsychological test data. Dr. Nelson will examine effects of antidepressants and a cognitively focused psychotherapy, Problem Solving Therapy, on cognition during treatment of late life depression.

Drs. Targum, Fava, and Iosefescu will present the results of different clinical trials that have examined change in cognition during treatment. The independence of change in cognition from change in depression will be examined and the effects of cognition on functioning will be considered. The discussant, Dr. Farchione, will present a perspective from the FDA.

Learning Objectives:

- Identify specific cognitive deficits associated with depressive disorder.
- Describe the clinical relevance of cognitive deficits in depression and the need, if any, for specific treatments.
- Describe differences between clinician rated neuropsychological assessments and patient perceptions of cognitive function.

INDIVIDUAL ABSTRACT:
COGNITIVE IMPAIRMENT IN LATE LIFE DEPRESSION: TYPE, FREQUENCY, AND METHODS OF ASSESSMENT

Scott Mackin
University of California, San Francisco

Cognitive impairment represents a commonly occurring and debilitating aspect of late life depression (LLD). Executive dysfunction and information processing speed deficits are often considered to be hallmark cognitive features of LLD; however impairments of memory, expressive language, and attention are also frequently reported. Given the heterogeneity of cognitive impairments exhibited by individuals with LLD differentiating the direct impact of LLD on cognition from the effects of other concurrent conditions, such as neurodegenerative disease, represents a significant challenge. Cognitive deficits are usually defined by neuropsychological test results that are compared with normative samples as well as a patient report of cognitive decline however there is variability in assessment methods and cognitive tests utilized in studies of LLD. Some of the common assessment methods and neuropsychological tests used in LLD studies will be reviewed. Further, we will present data on the incidence of cognitive impairments in a series of 100 patients with late life depression participating in an ongoing study. In our sample 60% of the sample exhibited at least one cognitive deficit. The most common deficits in this sample were in the domain of information processing speed (41%), memory (38%), executive dysfunction (35%), expressive language (25%), and abstract reasoning (18%). The majority of participants had cognitive deficit in one domain; however 35% of the sample exhibited deficits in two or more cognitive domains. Data on cognitive profiles will be presented. In late life depression, the relationship of patient perception of cognitive functioning with objective measures of cognition is relatively understudied. We will review the extant literature documenting previous studies evaluating patient perception of cognitive dysfunction in LLD. Further, we will present data on a new 20-item measure of patient perception of cognitive function in 50 participants with LLD in relation to objective measures of cognition.

Learning Objectives:

- To gain a better understanding of the relationships between cognitive impairment and depression in older adults.
- To promote understanding of the relationship between patient perception of cognitive function to objective measures of cognition in older adults with major depression.

Literature References:

• Mackin, RS, Nelson, C, Delucchi, K, Raue, P, Byers, A, Barnes, D, Satre, D., Yaffe, K, Alexopoulos, GS, & Areán, PA (in press). Cognitive outcomes following psychotherapeutic interventions for major depression in older adults with executive dysfunction. American Journal of Geriatric Psychiatry.Mackin, RS, Delucchi, K, Arean, PA, Mathews, C (2011). Cognitive functioning in older adults with depression and severe compulsive hoarding behaviors. International Journal of Geriatric Psychiatry, 26, 314-321.

INDIVIDUAL ABSTRACT:
EFFECTS OF TREATMENT ON COGNITION IN LATE LIFE DEPRESSION
Craig Nelson
UCSF
Late life depression (LLD) is frequently associated with cognitive impairment. These deficits may be secondary to the depression, may be associated with early neurodegenerative disease, or both. Prior antidepressant trials in this patient group will be briefly reviewed both in terms of common findings and assessment methods. One of these studies suggests that differentiating impaired from non-impaired patients appears to be important since the non-impaired patients show little change with treatment while the impaired patients improve but do not return to normal (Butters et al 2000). Change in cognition may be associated with change in depression, treatment assignment, or the interaction. For example in one trial processing speed improved with citalopram and placebo in depression responders but in non-responders drug treatment appeared to have an adverse effect (Culang et al 2009). New data from a controlled study of Problem Solving Therapy (PST) will be presented. These data are of interest because PST is a therapy that targets executive functioning in depression. 221 adults aged 60 years and older with MDD and evidence of executive dysfunction participated in a randomized trial comparing Problem Solving Therapy (PST) and Supportive Therapy (ST) for LLD. Cognitive performance on 7 tests of executive functioning, verbal learning, and memory was evaluated at baseline and after 12 weeks of treatment. The results of this study will be presented and the implications of the findings discussed.

Learning Objectives:
• Recognize cognitive deficits in late life depression.
• Describe the effects of treatment on cognition in late life depression.

Literature References:
• Butters MA et al. Changes in cognitive functioning following treatment of late-life depression. Am J Psychiatry 2000;157:1949-1954.
• Culang ME et al. Change in cognitive functioning following acute antidepressant treatment in late-life depression. Am J Psychiatry 2009;17:881-888.

INDIVIDUAL ABSTRACT:
CHANGES IN COGNITIVE SYMPTOMS BEFORE AND AFTER BUSPIRONE-MELATONIN TREATMENT FOR MAJOR DEPRESSIVE DISORDER
Steven D. Targum
Clintara, LLC
Specific cognitive deficits (loss of focus, mental sharpness, and word recall) are often associated with acute depressive episodes and contribute to the functional impairment seen in depressed

patients (apathy, loss of motivation, inattentiveness). Although these symptoms may resolve as the mood symptoms improve with antidepressant treatment, many patients sustain residual cognitive deficits that may be independent of the depressive diathesis and/or treatment-emergent side effects of the medication itself.
We tracked changes in specific cognitive deficits using the patient self-rated Cognitive and Physical Functioning Questionnaire (CPFQ) during a 6-week, double-blind, placebo-controlled trial of a combination treatment (buspirone 15 mg with melatonin-SR 3 mg) versus buspirone (15 mg) monotherapy in patients with acute major depressive disorder (MDD). We compared treatment response in each of the 3 groups to changes in the total CPFQ, cognitive factor score, and the 7 individual CPFQ items.
Using IDSc16 change scores, 23 of 54 patients (42.6%) were treatment responders in the combination group in contrast to 8 of 30 (26.6%) in the buspirone monotherapy group and 9 of 30 (30%) in the placebo group.
Changes in the total CPFQ scores were correlated with the IDSc16 in all 3 test groups ($r= 0.304$; $p= 0.001$). We examined treatment responders and non-responders separately in each test group. Improvement on the cognitive factor score was essentially the same in all 3 treatment responder groups. However, within the non-responder groups, the cognitive factor score improved significantly more with the combination treatment than with either buspirone monotherapy or placebo ($p= 0.03$). This preliminary finding suggests that the combination treatment may have had a differential effect on cognitive function distinct from the mood symptoms, and that that cognition may be a distinct target for treatment within a population of patients with MDD.

Learning Objectives:

- To examine possible antidepressant response differences between specific cognitive symptoms and mood symptoms in patients with acute major depressive disorder.
- To explore whether cognition represents a distinctive symptom cluster apart from other depressive symptoms in patients with major depression disorder.

Literature References:

- Fava M, Targum SD, Nierenberg AA, Bleicher LS, Carter TA, Wedel PC, Hen R, Gage FH, Barlow C. An Exploratory Study of Combination Buspirone and Melatonin SR in Major Depressive Disorder (MDD): A Possible Role for Neurogenesis in Drug Discovery, J Psychiat. Res. 46:1553-1563, 2012
- Targum SD, Wedel PC, Bleicher LS, Busner J, Daniel DS, Robinson J, Rauh P, Barlow C. A comparative analysis of centralized, site-based, and patient ratings in a clinical trial of Major Depressive Disorder. Journal Psychiatric Research. 47: 944-954, 2013

INDIVIDUAL ABSTRACT:
CHANGES IN COGNITIVE SYMPTOMS BEFORE AND AFTER VORTIOXETINE TREATMENT IN MAJOR DEPRESSIVE DISORDER

Maurizio Fava
Massachusetts General Hospital

Cognitive symptoms are common among patients with major depressive disorder (MDD) and even among responders to standard antidepressant therapies. We have found that difficulties with attention, concentration, and memory are reported by as many as 30-40% of patients.
Vortioxetine is a newly approved antidepressant with multi-modal activity, including elevating

brain levels of serotonin, acetylcholine, glutamate, dopamine, norepinephrine, and histamine. Preclinical data suggest a pro-cognitive effect of this compound and these findings have led to the investigation of its possible effects in depressed patients with cognitive symptoms. A double-blind study of elderly (≥65 years) depressed patients [NCT00811252] has shown distinct effects of vortioxetine compared to placebo and duloxetine in the digit symbol substitution test (DSST) and overall beneficial effects of this compound in multiple cognitive domains. A subsequent post-hoc analysis of a double-blind study in adults with MDD [NCT01163266] and cognitive symptoms [as defined by elevated scores of the Cognitive and Physical Functioning Questionnaire (CPFQ)] has shown significantly greater improvements than placebo on the cognitive factor score of the CPFQ. Two more recent double-blind studies, called FOCUS [NCT01422213] and CONNECT [NCT01564862], evaluated the cognitive effects of vortioxetine compared to placebo in MDD patients with depression, with CONNECT also including duloxetine. In this presentation, I will also review the results of these recently completed studies whose primary outcome measure is a composite score of the DSST and the Rey Auditory Verbal Learning Test (RAVLT) or the DSST, respectively. In addition, study patients are administered numerous other neurocognitive tests, the Montgomery-Åsberg Depression Rating Scale, self-reported measures of cognitive function, and a measure of performance-based functional capacity. Based on the findings on these studies, it would appear that the procognitive effects of vortioxetine observed preclinically are being translated into distinct and favorable clinical changes in depressed patients experiencing cognitive difficulties.

Learning Objectives:

- Participants will become familiar with the preclinical evidence of pro-cognitive effects of vortioxetine.
- They will also learn about the effects of vortioxetine on cognition among depressed patients with cognitive impairments.

Literature References:

- du Jardin KG, Jensen JB, Sanchez C, Pehrson AL. Vortioxetine dose-dependently reverses 5-HT depletion-induced deficits in spatial working and object recognition memory: A potential role for 5-HT1A receptor agonism and 5-HT3 receptor antagonism. Eur Neuropsychopharmacol. 2013 Aug 2. pii: S0924-977X(13)00182-X. doi: 10.1016/j.euroneuro.2013.07.001. [Epub ahead of print]
- Mørk A, Montezinho LP, Miller S, Trippodi-Murphy C, Plath N, Li Y, Gulinello M, Sanchez C. Vortioxetine (Lu AA21004), a novel multimodal antidepressant, enhances memory in rats. Pharmacol Biochem Behav. 2013 Apr;105:41-50. doi: 10.1016/j.pbb.2013.01.019. Epub 2013 Feb 1.

INDIVIDUAL ABSTRACT:
COGNITIVE DEFICITS IN MOOD DISORDERS: IMPACT ON FUNCTIONAL OUTCOMES AND TREATMENT STRATEGIES

Dan V. Iosifescu
Icahn School of Medicine at Mount Sinai

Multiple studies suggest that in both unipolar and bipolar mood disorders, acute mood episodes are characterized by impairment involving multiple cognitive domains, such as attention, memory and executive functions. However, longitudinal studies suggest a large proportion of

subjects also experience persistent cognitive deficits even after significant improvement of mood symptoms and during the remission phase of mood disorders. Patients with unipolar and bipolar mood disorders also experience significant functional impairment, which may be related to persistent neuropsychological deficits. We will present data from a study of 283 bipolar subjects where self-report cognitive deficits (measured with the Cognitive and Physical Functioning Questionnaire, CPFQ) and depression scores (MADRS) were independently associated with quality of life and functional outcome measures (Q-LES-Q, LIFE-RIFT). Treatment of such cognitive deficits thus becomes a significant focus of clinical interventions. We will review cognitive outcomes from several recent studies in mood disorders using glutamatergic modulators. In a group of 73 MDD subjects, ketamine improved cognitive symptoms (measured with MATRICS) but did not separate from the comparator midazolam. In a sample of 72 euthymic bipolar subjects treatment with memantine was associated with improved cognitive function (total RBANS score and RBANS indexes for attention, language and delayed memory) compared to placebo. In conclusions, cognitive deficits have an important impact on functional outcomes in mood disorders; pharmacological agents acting on the glutamatergic system could play an important role in their management.

Learning Objectives:

- Understand the independent impact of mood and cognitive deficits on functional outcomes in mood disorders.
- Describe cognitive outcomes in mood disorders after treatments with several glutamatergic modulators, such as ketamine and memantine.

Literature References:

- Iosifescu DV. The relation between mood, cognition and psychosocial functioning in psychiatric disorders. Eur Neuropsychopharmacol. 2012;22 Suppl 3:S499-504.
- Murrough JW, Wan LB, Iacoviello B, Collins KA, Solon C, Glicksberg B, Perez AM, Mathew SJ, Charney DS, Iosifescu DV, Burdick KE. Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response. Psychopharmacology (Berl). 2013 [Epub ahead of print]

WORKSHOP
4:45 PM – 6:45 PM

WORKSHOP OVERVIEW:
NEW APPROACHES TO FUNDING CLINICAL TRIALS AT NIMH

William Z. Potter[1], Meg Grabb[1], Jill Heemskerk[1], Christopher Sarampote[1], David J. Kupfer[2]
[1]NIMH, [2]University of Pittsburgh School of Medicine

The National Institute of Mental Health has just announced a series of new funding initiatives (R21/R33, Companion R33, U01 for Exploratory and Experimental Therapeutics; R01/R34 and Collaborative R01 for Effectives/Dissemination) to cover all future applications that involve any type of clinical trial. Each identifies opportunities for testing various interventional approaches with a focus on generation of data that can be used as a milestone for going to the next step in testing the relevant underlying hypothesis or disseminating a treatment. The details of what is asked for as well as the review process represent a significant change in expectations. We anticipate some confusion with the regard to both the basis for change and exactly what is

intended. A two hour workshop with at least 40 minutes protected for discussion is therefore proposed. The rationale and goals of each announcement will be briefly presented and potential issues highlighted to engage feedback, questions and comments from attendees. NIMH leadership (Dr. Insel with Wang as back up) will introduce the overall rationale followed by three 18 minute presentations: Dr. Margaret Grabb will present "First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders", Dr. Jill Heemskerk will present "Exploratory Clinical Trials of Novel Interventions for Mental Disorders" and Dr. Chris Sarampote will present, "Pilot Effectiveness Studies and Services Research Grants" and "Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions". Following specific questions to the presenters, Dr. David Kupfer will initiate an open discussion from the perspective of a potential academic applicant. We anticipate that there will be many questions as to the meaning of such terms as "target engagement" and the requirement for evidence of such, especially for those interventions that cannot be easily quantified in terms of brain effects such as degree of occupancy of a receptor with a PET ligand. As conceptualized at the NIMH there are many ways to relate any class of intervention to engaging some mechanism or process (the "target") – examples will be provided. The aim is to solicit study proposals that provide some quantifiable measure of such engagement between the intervention (drug, device or psychosocial) and the clinical outcome measure in order that any underlying hypothesis can be provisionally rejected when one establishes that the proximal target was affected without seeing the desired clinical effect. The backdrop for this focus are decades of negative studies that are argued to be uninterpretable because the wrong "dose" of the intervention was given.

WORKSHOP
4:45 PM – 6:45 PM

WORKSHOP OVERVIEW:
PSYCHOPHARMACOLOGY OF RESIDUAL SYMPTOMS IN MOOD DISORDERS AND SCHIZOPHRENIA

Jonathan Alpert[1], Donald C. Goff[2], Michael E. Thase[3], Thomas Laughren[4], Goldberg F. Joseph[5]
[1]Massachusetts General Hospital, Harvard Medical School, [2]NYU Medical School, [3]Perelman School of Medicine of the University of Pennyslvania, [4]MGH CTNI, [5]Icahn School of Medicine at Mount Sinai

Residual symptoms among individuals with mood disorders and schizophrenia are ubiquitous and clinically meaningful targets for novel pharmacological strategies given their strong association with poorer outcomes during long-term follow-up including higher relapse rates and chronic psychosocial impairment. Nevertheless, while there is a compelling need for more effective treatment strategies for residual symptoms there are also unique challenges involved in the design of clinical trials intended to address these problematic but often sub-syndromal symptoms. Moreover, the high rates of persistence of particular residual symptoms despite optimization of initial treatment may underscore the need to recruit molecular mechanisms other than those leveraged by first-line pharmacotherapy. This panel will discuss conceptual and methodological issues related to the study of residual symptoms in depression, bipolar disorder and schizophrenia as well as present promising avenues for drug development. As pharmacological augmentation is often the preferred initial approach to residual symptoms, Dr. Laughren will describe core methodological issues related to augmentation trials in mood disorders and schizophrenia. Dr. Goff will present experience with a range of pharmacological

targets for residual symptoms in schizophrenia, particularly those associated with chronic cognitive deficits and negative symptoms, and will discuss why drug discovery based on classical models of these domains has met with limited success. Dr. Goldberg will then discuss the relevance of residual symptoms in bipolar disorder for course of illness and adjunctive strategies for persistent mood symptoms. Dr. Thase will focus on pharmacotherapy of residual symptoms in unipolar major depressive disorder and highlight particular symptoms including fatigue that often fail to respond adequately to antidepressants. ·

Learning Objectives:

- To become familiar with the methodological and conceptual issues related to the study of residual symptoms in mood disorders and schizophrenia.
- To understand how new molecular targets may provide novel therapeutic approaches to the study of residual symptoms.

INDIVIDUAL ABSTRACT:

METHODOLOGICAL AND DESIGN ISSUES IN AUGMENTATION TRIALS

Thomas Laughren
MGH CTNI

Initial drug treatments for depression and schizophrenia frequently do not produce optimal control of symptoms. Clinicians are faced with several choices to address such patients, one of which is augmentation with another agent, but they have little systematic data upon which to base treatment decisions. This presentation will approach augmentation trials from a design and methodological perspective, including regulatory concerns that must be addressed. Distinctions will be made between the different possible goals of such programs, including both timing of response and enhancement of response, as well as between overall enhancement of the targeted syndrome and more targeted enhancement of "residual" symptoms. Different approaches will be proposed for the timing of such augmentation strategies, e.g., at initiation of treatment for new patients, for patients with suboptimal responses, or for residual phase patients. The difficult issue of distinguishing between suboptimal responders and treatment resistant patients will also be discussed. Different study designs will be proposed for addressing these complex challenges and the challenges posed by regulatory agencies, including the issue of possible pseudo-specificity.

Learning Objectives:

- Understanding the different goals of augmentation strategies
- Understanding different study designs that can be used to explore augmentation approaches.

Literature References:

- Khin NA, Chen YF, Yang Y, Yang P, Laughren TP. Exploratory analyses of efficacy data from schizophrenia trials in support of new drug applications submitted to the US Food and Drug Administration. J Clin Psychiatry. 2012 Jun;73(6):856-64.
- Khin NA, Chen YF, Yang Y, Yang P, Laughren TP. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry. 2011 Apr;72(4):464-72.

INDIVIDUAL ABSTRACT:

NEW APPROACHES TO THE TREATMENT OF RESIDUAL SYMPTOMS OF SCHIZOPHRENIA

Donald C. Goff
NYU Medical School

Residual negative symptoms and cognitive deficits are common in schizophrenia and are major contributors to disability. The current status of evidence-based treatments for symptoms refractory to antipsychotics will be reviewed. New therapeutic strategies will be discussed, including emerging approaches to facilitate neuroplasticity and personalized medicine approaches based on genetic markers. Specific examples will include D-cycloserine treatment of negative symptoms and delusions, folate supplementation for negative symptoms, and cognitive remediation. Finally, new models to guide treatment development will also be presented.

Learning Objectives:

- Review new approaches to the treatment of negative symptoms.
- Review new approaches to the treatment of cognitive deficits associated with schizophrenia.

Literature References:

- Goff DC, Hill M, Barch D. The treatment of cognitive impairment in schizophrenia. Pharmacol Biochem Behav. 2011 Aug;99(2):245-53. PMID: 21115035
- Goff DC. Future perspectives on the treatment of cognitive deficits and negative symptoms inschizophrenia. World Psychiatry. 2013 Jun;12(2):99-107. doi: 10.1002/wps.20026. PMID:23737409

INDIVIDUAL ABSTRACT:
RESIDUAL SYMPTOMS IN BIPOLAR DISORDER: THE ROLE OF POLYPHARMACY

Goldberg F. Joseph
Icahn School of Medicine at Mount Sinai

This presentation will summarize current knowledge about the prevalence and impact of residual affective symptoms on the course and outcome of bipolar disorder as well as the literature on specific combination drug therapies aimed to minimize or treat residual symptoms. Manic-depressive illness has classically been described, and differentiated from schizophrenia, based partly on its distinct periodicity and recovery patterns between discrete episodes. Yet, modern follow-up studies indicate that a majority of individuals with bipolar disorder have incomplete remissions and encounter residual or subsyndromal symptoms that may contribute importantly to overall disability. Persistent residual affective, cognitive or anxiety symptoms after an index manic or depressive episode have been associated with poorer lesser prophylactic efficacy of mood stabilizers, a faster time until relapse or recurrence, poorer treatment adherence, and impaired work and social functioning. As compared to other areas of medicine, remarkably few intervention studies have formally and specifically targeted residual symptoms, or examined the safety and efficacy of combination drug therapies as strategies to achieve more robust remissions. Certain residual symptoms may be important to inform subsequent pharmacology decisions (e.g., residual mania symptoms predict poorer relapse prevention with lamotrigine). Some mood stabilizing agents exert more pronounced antimanic than antidepressant properties (or vice-versa) and, as such, may be incorporated more strategically within a multi-drug treatment regimen; certain agents also may be especially useful for their potential efficacy

against specific target symptoms (e.g., lithium and suicide risk; divalproex and impulsivity/aggression; gabapentin and anxiety). Augmentation strategies involving certain anticonvulsants (e.g., carbamazepine or oxcarbazepine, divalproex) may offer particular efficacy for residual mood symptoms, while a number of adjunctive atypical antipsychotics have received increasing attention and empirical study to achieve more robust acute remissions in bipolar mania or depression than may occur with a traditional mood stabilizer alone.

Learning Objectives:

- To describe the nature and extent of residual, subsyndromal inter-episode symptoms in bipolar disorder and their impact on relapse and functional outcome.
- To discuss evidence based treatment strategies for minimizing incomplete remissions and targeting residual symptoms in bipolar disorder.

Literature References:

- Goldberg JF, Calabrese JR, Saville BR, et al. Mood stabilization and destabilization during acute and continuation phase treatment for bipolar I disorder with lamotrigine or placebo. J Clin Psychiatry. 2009; 70: 1273-80.
- Altshuler LL, Post RM, Black DO, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J Clin Psychiatry 2006; 67: 1551-1560.

INDIVIDUAL ABSTRACT:
STUDYING THE EFFICACY OF ADJUNCTIVE THERAPIES FOR DEPRESSIVE DISORDERS

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

About one third of those who respond to a 6-8 week course of antidepressant therapy will have too many persistent or residual symptoms to meet criteria for remission. For many patients, these persistent symptoms take a toll on quality of life and impair functional status. Residual depressive symptoms among patients who have responded to antidepressant therapy are thus an appropriate target for treatment development. This portion of the workshop will describe the most common residual symptoms observed among people with incompletely remitted depression and will provide an overview of the major treatment options that are currently used. The 'best practice' research methods to maximize signal detection in controlled studies will be summarized and pitfalls that sometimes adversely affect signal detection will be discussed.

Learning Objectives:

- Learn the most common residual symptoms among patients who have responded to antidepressant therapy.
- Become familiar with the pros and cons of the most commonly used research designs to study adjunctive therapies.

Literature References:

- McClintock SM, Husain MM, Wisniewski SR, Nierenberg AA, Stewart JW, Trivedi MH, Cook I, Morris D, Warden D, Rush AJ.Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. J Clin Psychopharmacol. 2011

Apr;31(2):180-6Thase ME.Update on partial response in depression. J Clin Psychiatry. 2009;70 Suppl 6:4-9

PLENARY SESSION
8:15 AM – 9:45 AM

KEYNOTE SESSION: NEW APPROACHES TO MENTAL ILLNESS IN THE ERA OF THE NATIONAL BRAIN INITIATIVE
Chair: *Husseini K. Manji, M.D., Ph.D., Johnson & Johnson*
Speakers: *Thomas Insel M.D., NIMH*
Patrick Kennedy, Former US Representative & Mental Health Activist
Brain disorders are among mankind's most devastating illnesses. Worldwide, they place an enormous societal burden on those affected. Indeed, in the United States alone this burden of illness is rapidly approaching $1 trillion annually, a number that is only likely to escalate in coming years with the aging population. In this plenary session, Drs. Manji and Insel and Mr. Kennedy will discuss interrelated facets in our search to better understand the mechanisms underlying a wide range of mental illnesses and to develop effective new treatments for them. Rapid advances in science and technology over the past decade have provided us with an unprecedented opportunity and the tools needed to unlock the secrets of the brain. Dr. Insel will discuss the many significant advances that have recently been made towards understanding serious mental illnesses. Although public and private resources devoted to research in this area are diminishing, a host of cutting-edge approaches—from genomics to data mining, proteomics to biomarkers, pathway modeling to protein engineering, neuroimaging to optogenetics—is nevertheless revolutionizing the way we think about, study, and approach the development of urgently needed novel treatments for mental disorders, with extremely promising results.
Dr. Manji will discuss the paradigm shift that must accompany future research in this area. This includes not only moving from a 'diagnose and treat' approach to a 'predict and pre-empt' model, but the need to develop novel solutions that encompass meaningful and measurable patient outcomes (for instance, the ability to rapidly resume social and work responsibilities). Mr. Kennedy will discuss the many social issues that can and must be addressed in any "whole-world" view of mental illness, including parity for mental health, ending the discrimination against patients, and the travesty of homeless and imprisoned individuals suffering from mental disorders.
The session will emphasize the speakers' commitment to a strong, united, cross-disciplinary approach towards a key common goal: to work together across industry, academia, government, and the private sector in a concerted effort to improve the lives of the millions of individuals affected by brain disorders. With such a cooperative effort, real, tangible progress can be made.

PLENARY SESSION
10:00 AM – 12:00 PM

NIH INSTITUTE DIRECTORS
Chair: *David Kupfer M.D., University of Pittsburgh School of Medicine*
Speakers: *Thomas Insel M.D., NIMH*
Phil Skolnick Ph.D., NIDA
Kenneth Warren Ph.D., NIAAA

Josephine Briggs M.D., NCCAM
Christopher Austin M.D., NCATS
Richard Nakamura Ph.D., CSR

This year's Institute Director's session will bring together directors from various NIH institutes who all have a similar goal of searching for new approaches in the research of mental disorders. Each director will have ten minutes to discuss what activities are going on within their institute regarding this goal. Thomas Insel, NIMH Director, will begin the session discussing transformation of clinical trials. Phil Skolnick will discuss one of the more challenging issues that NIDA faces are the epidemic of (both prescription and non-prescription) opiate abuse. To put the problem in perspective, it has been estimated that there are 3 million Americans currently abusing opioids; more deaths result from opiate overdose than from firearms. He will overview NIDA's efforts to combat both opiate abuse and overdose deaths. Kenneth Warren of NIAAA will discuss the current framework for medications development of alcohol use disorders. Josephine Briggs will discuss NCCAM's interest in encouraging work on the neuroscience of the mind-body interface and the mechanisms by which meditative practices such as mindfulness, hypnosis, and meditative exercise forms may impact on pain processing. Christopher Austin will address NCATS' unique role in the biomedical ecosystem and the translational science problems being prioritized by NCATS. He will also give an overview of the Center's programs and collaborative opportunities. Finally, Richard Nakamura will discuss the Center for Scientific Review's steps to measure and improve the performance of peer review. The session will continue with an open dialogue Q&A session with audience interaction.

PLENARY UPDATES SESSION
2:00 PM – 3:30 PM

OVERALL ABSTRACT:
THE LATEST ON TREATMENT OF MOOD, OCD-SPECTRUM, AND BINGE EATING DISORDERS

Chair: *Maurizio Fava, Massachusetts General Hospital*

Recent advances in clinical neuroscience have led to the development of novel treatments of mood, OCD-spectrum, and binge eating disorders. The purpose of this symposium is to provide an overview of the latest developments in the pharmacological treatments for these conditions. Dr. Papakostas will review new approaches to the treatment of depression, as well as to the identification of subpopulations of depressed patients more likely to benefit from a given treatment. Dr. Ketter will present an update on new therapeutic developments in the treatment of bipolar disorder, such as the approval by the FDA of asenapine, risperidone long-acting injectable (LAI), ziprasidone, aripiprazole, and lurasidone therapy for bipolar disorder. In addition, Dr. Ketter will discuss the International Society for Bipolar Disorders (ISBD) Antidepressant Use in Bipolar Disorders Task Force controversial report from 2013. Finally, Dr. Ketter will present data concerning some novel pharmacological treatments for bipolar disorder. Dr. McElroy will also provide an overview of the treatments for hoarding disorder and binge eating disorder, new discrete diagnostic entities in DSM-5. Psychological treatments are effective for both conditions, but not all patients respond and pharmacotherapy is emerging as an important treatment option. Serotonin reuptake inhibitors have been the most widely studied agents, but both conditions respond modestly at best to these compounds. Newer agents showing

promise include antiepileptics and psychostimulants. Available research on the pharmacotherapy of HD and BED will be reviewed, and future directions will be discussed.

INDIVIDUAL ABSTRACT:
HOARDING DISORDER AND BINGE EATING DISORDER
Susan McElroy
University of Cincinnati College of Medicine
Hoarding disorder (HD) and binge eating disorder (BED) are each important public health problems that are new discrete diagnostic entities in DSM-5, which should help in identifying individuals who need help as well as new treatments strategies. Psychological treatments are effective for HD and BED, but not all patients respond and pharmacotherapy is emerging as an important treatment option for both conditions. Serotonin reuptake inhibitors have been the most widely studied agents, but both conditions respond modestly at best to these compounds: HD may respond less well than obsessive compulsive disorder does to SRIs and, though helpful for associated depressive symptoms, SRIs are not associated with weight loss in BED, which is often associated with overweight or obesity. Newer agents showing promise include antiepileptics and psychostimulants. Available research on the pharmacotherapy of HD and BED will be reviewed, and future directions will be discussed.

INDIVIDUAL ABSTRACT:
UPDATE ON BIPOLAR DISORDER PHARMACOTHERAPY
Terence Ketter
Stanford University School of Medicine
Although the pace of treatment advances in bipolar disorder pharmacotherapy has attenuated somewhat in the 2010s compared to the early to mid-2000s, there have continued to be important new therapeutic developments. Thus, the United States Food and Drug Administration (US FDA) has approved asenapine monotherapy and adjunctive (added to lithium or valproate) therapy for acute manic and mixed episodes, and risperidone long-acting injectable (LAI) formulation monotherapy and adjunctive therapy and ziprasidone adjunctive therapy for bipolar maintenance (in 2009-2010), as well as aripiprazole adjunctive therapy (added to lithium or valproate) for bipolar maintenance in 2011, and lurasidone monotherapy and adjunctive (added to lithium or valproate) therapy for acute bipolar I depression in 2013. In addition, multicenter, randomized, double-blind placebo controlled trials have assessed the utility of ziprasidone monotherapy and adjunctive therapy, olanzapine monotherapy, and armodafinil adjunctive therapy in acute bipolar depression, cariprazine monotherapy and paliperidone monotherapy and adjunctive therapy in acute mania, and paliperidone monotherapy and aripiprazole adjunctive therapy (added to lamotrigine) for bipolar maintenance. Moreover, the International Society for Bipolar Disorders (ISBD) Antidepressant Use in Bipolar Disorders Task Force published its' report on this controversial topic in 2013. Finally, there has been increasing appreciation of the potential for rapid relief of depression with interventions that affect glutamatergic neurotransmission such as ketamine, although to date, such interventions remain only research (as opposed to clinical) tools.

INDIVIDUAL ABSTRACT:
UPDATE ON TREATMENT OF MAJOR DEPRESSIVE DISORDER
George I. Papakostas

Massachusetts General Hospital, Harvard Medical School
Major Depressive Disorder (MDD) is a serious, debilitating, life-shortening illness that affects many persons of all ages and backgrounds. MDD is also a treatable illness, with pharmacological agents along with various forms of psychotherapy representing the cornerstone of treatment. However, for many patients suffering from MDD, treatments delivered do not always have the desired effect. Therefore, it remains crucial for the field to aid in the development of new and more efficacious antidepressant therapies. Another possible approach towards the development of novel therapeutic strategies for MDD involves identifying subpopulations of depressed patients (with the use of mediators of outcome) that are more likely to experience the benefits of a given (existing) treatment versus placebo, or versus a second treatment. The present talk will review developments in these two key areas over the course of the past 12 months.

WORKSHOP
3:45 PM – 5:45 PM

WORKSHOP OVERVIEW:
NEW APPROACHES TO DRUG STUDIES FOR TREATING SOCIAL DEFICITS IN AUTISM SPECTRUM DISORDER

Meg Grabb[1], Ann Wagner[1], Lawrence Scahill[2], Bryan H. King[3], Alessandro Bertolino[4], James T. McCracken[5], Warren Jones[6]
[1]NIMH/NIH, [2]Emory University, [3]Seattle Children's Hospital and University of Washington, [4]F. Hoffmann-La Roche Ltd, UCLA Semel Institute[5], Marcus Autism Center[6]
Two medications, risperidone and aripiprazole, are approved by the US Food and Drug Administration for the treatment of irritability in children age 5 to 17 with DSM-IV autistic disorder. However, there are no approved medications for the core symptoms of autism spectrum disorder (ASD), including social disability or repetitive behavior. In fact, pharmacological clinical trials in ASD have yielded mixed results in efficacy. The overall goal of this workshop is to present opportunities for designing early stage pharmacological trials differently from the past, in the hopes of successfully developing treatments for the core symptoms of ASD. This scientific panel will present a series of talks outlining the central issues facing drug development in ASD: the current state of assessment tools being used in clinical trials, strategies in making compound selections, and the importance of biomarkers and other objective measures. This workshop will specifically focus on one core symptom of ASD: targeting social deficits. Drs. Meg Grabb and Ann Wagner will initiate this interactive session highlighting the new priorities of NIMH in pharmacological trial design as well as the Interagency Autism Coordinating Committee (IACC) priorities. Dr. Larry Scahill will then discuss available instruments for measuring outcome in ASD clinical trials, focusing on strengths and weaknesses of measures for evaluating outcome in the social domain. Although the biological differences in people with ASD are still largely unknown, there is some evidence for different neurotransmitter systems to be altered, providing an opportunity for selecting a range of investigational compounds for testing. Dr. Jim McCracken will present strategies for selecting these compounds based on his experience leading the NIMH contract to conduct "experimental medicine" types of trials in ASD. Once compound selection has taken place, biomarkers can be incorporated into the protocol for use in stratifying subjects and/or assessing treatment response. Dr. Bryan King will present the latest data on the use of brain measures such as EEG and fMRI to help inform the compound's CNS action. Dr. Warren Jones will then present his research on designing novel ways of capturing social behavior objectively, and how these measures could be incorporated into future trial designs. Finally, Dr.

Alessandro Bertolino will lead the discussion by summarizing the gaps and the opportunities for incorporating new designs into AS trials, from an industry perspective. Each presentation is followed with a 10 minute session for Q&A. The presentations are designed to build sequentially: 1) presenting the state of assessment tools to measure social outcomes in ASD trials, (2) how to identify a promising compound to test, (3) how would to use biomarkers to evaluate CNS activity, and (4) objective measures that can be used as early indicators of a core behavior, like social interaction. This series of talks highlights new avenues for conducting pharmacological trials in subjects with ASD. These new pathways may deviate from traditional models and we expect it will raise many questions from the audience throughout the session.

Learning Objectives:

- Gaps and new approaches to drug studies in autism spectrum disorder (ASD).
- Opportunities for incorporation and prioritization of biomarkers for ASD trials.

INDIVIDUAL ABSTRACT:
MEASURING SOCIAL DISABILITY IN AUTISM SPECTRUM DISORDER

Lawrence Scahill
Emory University

The Centers for Disease Control recently reported that Autism Spectrum Disorder (ASD) affects as many as 11 per 1000 children. This estimate reflects a considerable increase in the detected prevalence of ASD. In the DSM 5, ASD is defined by deficits in social communication as well as impairment due repetitive behaviors and restricted interests. There are no approved treatments and meager empirical support for treating these core features of ASD. In addition to the need for compounds targeting social communication or repetitive behavior, there is incomplete consensus on how to measure these outcomes in ASD. For example, can the same measure be used across the lifespan or across the wide range of intellectual ability observed in ASD. This presentation examines the strengths and weaknesses of five instruments (Aberrant Behavior Checklist - Social Withdrawal subscale; Behavior Assessment System for Children, Social Responsiveness Scale, Anxiety Depression and Mood Scale, Vineland Adaptive Behavior Scales) that have been used or considered to measure social outcomes in ASD.

Learning Objectives:

- At the conclusion of the presentation, participants will be able to identify five plausible measures of social disability in autism spectrum disorders.
- At the conclusion of the presentation, participants will recognize the current prevalence and defining features of autism spectrum disorders.

Literature References:

- Scahill, L., Hallett, V., Aman, M., McDougle, C. J., Arnold, L. E., McCracken, J. T., Tierney, E., Dziura, J., Deng, Y., & Vitiello, B. (2012). Brief report: Social disability in Autism Spectrum Disorder: Results from Research Units on Pediatric Psychopharmacology (RUPP) Autism Network Trials. Journal of Autism and Developmental Disorders, 43(3), 739-746.
- Hallett, V., Lecavalier,L., Sukhodolsky, D.G., Cipriano,N., Aman, M.G., McCracken, J.T., McDougle,C.J., Tierney,E., King,B.H.,Hollander, E.,Sikich,L., Bregman,J., Anagnostou,E. Donnelly,C.,Katsovich, L.,Dukes, K.,Vitiello,B., Gadow, K., & Scahill, L. (2013). Exploring the

manifestations of anxiety in children with Autism Spectrum Disorders. Journal of Autism and Developmental Disorders (online ahead of print, DOI 10.1007/s)

INDIVIDUAL ABSTRACT:
HONING IN ON TARGETS FOR COMPOUND SELECTION IN ASD TRIALS: THE NIMH FAST-ASD NETWORK

James T. McCracken
UCLA Semel Institute

Background: Pharmacologic clinical trials in autism spectrum disorders (ASD) and related disorders aiming for changes in core domains have been disappointing. Despite progress in ASD genetics, animal models, and neurobiology, the identification of compelling targets for ASD clinical trials has been a challenge. Objective: The aim of this presentation is to present a critique of current approaches to target selection, and to offer new recommendations for drug development efforts in ASD. Methods: The talk will present the approach taken by the NIMH in the recently launched "Fast Fail Trials in Autism Spectrum Disorders (FAST-AS)" which is designed to identify promising compounds for ASD and arrive at rankings of nominated targets. First, a critique and review of recent disappointing targeted treatments trials will be reviewed. Next, the FAST-AS compound selection process will be described by the review of one example of a highly ranked target in the GABA system. Aspects of trial design related to this approach will also be discussed. Results: There are a number of promising targets for investigation in ASD, some with very strong evidence implicating their relevance to core domains of the ASD phenotype. After discussing the model for target selection, we will describe the approach chosen for the first NIMH FAST-AS clinical trial. The GABA system emerges as a compelling target with links to core and associated features of ASD. Conclusions: With information from many sources rapidly accumulating as to the pathophysiology of ASD, the options for target selection are many. However, the field needs to modify its approach to target choice and trial design to capitalize on progress in basic and clinical understanding of this disorder.

Learning Objectives:
- The learner will be able to describe approaches to reducing heterogeneity in ASD trial subjects.
- The learner will appreciate the rationale for trials of GABAA agonists in ASD.

Literature References:
- Coghlan S, et al Neurosci Biobehav Rev, 2012
- Paul S, et al Nature Drug Develop, 2010

INDIVIDUAL ABSTRACT:
INCORPORATING POTENTIAL FUNCTIONAL BIOMARKERS IN CLINICAL TRIALS IN ASD

Bryan H. King
Seattle Children's Hospital and University of Washington

GABA abnormalities have been hypothesized to be associated with some manifestations of the ASD phenotype, including social deficits, propensity for seizures, anxiety, and even cognitive deficits. As animal models are generated based on genes identified for their association with ASD, GABA systems have been implicated in theories of excitatory and inhibitory imbalance in brain processes and thus for their potential as therapeutic targets. Within the heterogeneity of

ASD, the ability to identify potential subgroups of individuals for whom GABAergic interventions might be most appropriate could be a particular advantage for clinical trials. Thus far, efforts to assay GABA in vivo in ASD are limited, but findings generally do support hypothesized reduced GABAergic tone. Using MRS, various investigators have shown, for example, that regional variations exist in brain GABA concentration (expressed as GABA/Creatine ratio) in ASD relative to controls.
Cortical electrical activity measured by EEG and MEG has also been investigated as a potential translational biomarker for examining possible GABA deficits in autism and related disorders. Changes in both resting and activated neuronal network oscillatory activity across various frequency bands have been described. In addition, the effects of pharmacologic intervention can be detected using EEG, and are being investigated as possible probes of drug mechanism.

Learning Objectives:

- To appreciate the potential to utilize strategies like EEG and imaging to identify subgroups within the population with ASD for particular therapeutics.
- To highlight the potential to utilize strategies like EEG to identify target engagement in clinical trials in ASD.

Literature References:

- Gaetz W, Bloy L, Wang DJ, Port RG, Blaskey L, Levy SE, Roberts TP. GABA estimation in the brains of children on the autism spectrum: Measurement precision and regional cortical variation. Neuroimage. 2013 May 24. pii: S1053-8119(13)00568-5. doi: 10.1016/j.neuroimage.2013.05.068. [Epub ahead of print]
- Thatcher RW, North DM, Neubrander J, Biver CJ, Cutler S, Defina P. Autism and EEG phase reset: deficient GABA mediated inhibition in thalamo-cortical circuits. Dev Neuropsychol. 2009;34(6):780-800. doi: 10.1080/87565640903265178.

INDIVIDUAL ABSTRACT:

EYE-TRACKING MEASURES OF SOCIAL DISABILITY AS OUTCOME MEASURES IN SCHOOL-AGE CHILDREN WITH ASD

Warren Jones
Marcus Autism Center

Drug development focused on the social deficits in autism spectrum disorder (ASD) faces two obstacles: the heterogeneity of the phenotype and objective measurement of social disability. Our group has been developing and adapting existing eye-tracking technologies to quantify the degree of social disability in ASD and to measure change with treatment. Accurate quantitative measurement of social disability may be used to reduce sample heterogeneity by setting a level of disability for study inclusion. Eye-tracking measures may also be useful as study endpoints. Thus, eye-tracking technologies may be especially relevant for early drug treatment studies where precision of measurement is critical. In this presentation, we will describe contemporary eye-tracking technologies, provide evidence for the convergent validity, reliability and precision, of eye-tracking in children with ASD. The study sample consisted of 42 typically developing children (TD, mean age=9.61 years) and 128 children with ASD (mean age=10.55 years). Subjects were asked to watch naturalistic scenes of social interaction. Preliminary analyses focused on attention percent time looking at the eyes of others on screen. Children with ASD spent significantly less time looking at the eyes than TD peers (M(SD) = 32.3(17.8)% for ASD vs. 39.9(18.2)% for TD, $F = 51.8$, $p<0.05$). Test-retest correlation was solid: $r = 0.619$ for TD

and r =0.624 for ASD. The measures were collected with a greater than 88% success rate, and with measurement accuracy of less than 3 degrees of visual angle. Future analyses will consider more temporally sensitive measures such as looking at the eyes at socially salient moments.

Learning Objectives:

- Describe contemporary eye-tracking technologies.
- Evaluate evidence for the convergent validity, reliability, and precision of eye-tracking measures of social disability as potential outcome measures for study endpoints.

Literature References:

- Jones W & Klin A. (2013) Attention to eyes is present but in decline in 2-6 month-olds later diagnosed with autism. Nature.Rice K, Moriuchi JM, Jones W, Klin A. (2012) Parsing heterogeneity in autism spectrum disorders: visual scanning of dynamic social scenes in school-aged children. J Am Acad Child Adolesc Psychiatry. 51(3):238-48. PMID: 22365460
- Shultz S, Klin A, & Jones W. (2011) Inhibition of Eye Blinking Reveals Subjective Perceptions of Stimulus Salience. Proceedings of the National Academy of Sciences USA. 108(52):21270-5. PMID: 22160686

WORKSHOP
3:45 PM – 5:45 PM

WORKSHOP OVERVIEW:
NOVEL MECHANISMS OF ACTION FOR THE TREATMENT OF DEPRESSION AND ANXIETY: SCIENTIFIC UPDATES

Timothy Petersen[1], James W. Murrough[2], Dan V. Iosifescu[2], Sanjay Mathew[3], Jaskaran Singh[4], Michael R. Liebowitz[5]
[1]Clintara, LLC, [2]Icahn School of Medicine at Mount Sinai, [3]Baylor College of Medicine, [4]Janssen Research and Development, LLC, [5]Pherin Pharmaceuticals

Despite a wide array of available first line pharmacologic treatments for depression and anxiety, all too often patients do not experience full symptomatic relief (i.e., remission). Additionally, delay in onset of beneficial effects, as well as potentially bothersome side effects, highlight the limitations of commonly used pharmacologic interventions. Rates of adequate response to next step treatments are disappointingly low, and empirical evidence offers little to guide a clinician's choice, once initial treatment has failed. Fortunately, recent research suggests that several new treatment strategies, based on novel mechanisms of action, may offer patients greater hope for full symptom remission, more rapid speed of response, and less burdensome side effects. The primary purpose of this workshop is to provide a scientific overview of the rationale and evidence for several novel approaches to the treatment of depression and anxiety. Through focused didactic presentations and facilitated faculty-audience discussion, this workshop aims to enhance participants' knowledge base of this exciting area of clinical research and application. During this three-hour workshop, five subject matter experts will deliver presentations. Each presentation will be followed by a question and answer session that is complemented by audience polling data, gathered prior to the beginning of the lecture. Dr. Sanacora will present data based on his pre-clinical work, with a focus on what mechanisms hold the greatest promise for clinical application in mood and anxiety disorders. Dr. Murrough will provide a review of the rationale for the use of ketamine, an exciting glutamatergic treatment. In discussing evidence for

the safety and efficacy of ketamine, Dr. Murrough will also explain the potential advantages of intranasal administration. Dr. Liebowitz will provide the background of and evidence for the use of pherines for the treatment of depression and anxiety, including intranasal administration. Dr. Mathew's lecture will focus on evidence that suggests new treatment mechanisms may be able to provide rapid relief from suicidality, the most life threatening symptom of depression. Finally, Dr. Iosifescu will review evidence to support the use of various device-based treatments for mood disorders. The final component of this workshop will be an interactive discussion between all faculty members and workshop participants, to be facilitated by the workshop discussant.

Learning Objectives:

- Understand the rationale, mechanisms and evidence base for several novel treatments in development or in their early stages of use for the treatment of depression and anxiety.
- Describe the unique methodological and measurement challenges inherent in carrying out clinical research with these novel treatments.
- Become familiar with the most promising future molecular targets related to the development of treatments for depression and anxiety.

INDIVIDUAL ABSTRACT:
A REVIEW OF PRE-CLINICAL DATA

Gerard Sanacora
Yale University

The results of several large "real world" clinical studies, including the STAR*D, STEP-BD, CATIE and others, have highlighted the limitations of our currently available treatments for psychiatric disorders. These results have helped motivate us to reconsider how we conceptualize psychiatric illnesses. They have also provided a mandate to seek a greater understanding of the underlying pathogenesis and pathophysiology of these disorders in the pursuit of developing more effective treatment and prevention strategies. Although there is little definitive evidence of specific pathogenic or pathophysiological mechanisms tied to any individual psychiatric disorder, there is relatively wide agreement that high levels of life-stress, either in childhood or as an adult, are associated with the onset and/or exacerbation of a wide range of neuropsychiatric and general medical disorders. In light of the relationship between life-stress and mood/anxiety disorders, it is proposed that rodent models of chronic stress can be used to examine the underlying pathogenesis and pathophysiology of the disorders at the cellular, circuit, and behavioral levels. Increasing evidence suggests stress, both acute and chronic, has a variety of effects on the function of the glutamatergic neurotransmitter system in brain regions relevant to cognition, emotion and arousal. Stress-induced changes in presynaptic glutamate release, glutamate receptor activation and glial mediated glutamate clearance have all been demonstrated and have been implicated in the pathogenesis of several stress related neuropsychiatric disorders. This presentation will discuss the similarities between the cellular, physiological, and behavioral changes that are seen in rodents following chronic stress exposure and humans with mood and anxiety disorders. Considering the stress-induced changes in glutamatergic neurotransmitter system function, novel pharmacological targets have been identified. Preclinical data examining the effects of several novel agents targeting various points within the glutamatergic neurotransmitter including ionotropic (NMDA and AMPA) receptors, group I and II metabotropic receptors, and glutamate transporters will be discussed. New data using pharmacological and genetic approaches to evaluate the role of the glutamatergic system in mediating stress sensitivity and resiliency will be presented. These findings will be placed in the

context of several early phase clinical trials examining the efficacy and safety of several drugs targeting similar components of the glutamatergic neurotransmitter system.

Learning Objectives:

- To consider the rationale and validity of using preclinical rodent models in the development on novel therapeutic agents for mood and anxiety disorders.
- To discuss the results of recent preclinical studies examining the efficacy of novel drugs targeting several aspects of the glutamatergic system in rodent tests of antidepressant- and anxiolytic-like activity.

Literature References:

- M. Popoli, Z. Yan, B. S. McEwen, G. Sanacora, The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. Nature reviews. Neuroscience 13, 22 (Jan, 2012).
- G. Sanacora, M. Banasr, From pathophysiology to novel antidepressant drugs: glial contributions to the pathology and treatment of mood disorders. Biological psychiatry 73, 1172 (Jun 15, 2013).

INDIVIDUAL ABSTRACT:
KETAMINE: RATIONALE, EMPIRICAL EVIDENCE AND NEW ROUTES OF DELIVERY

James W. Murrough
Icahn School of Medicine at Mount Sinai

Background: Current treatments for major depression are only partially effective and exhibit a substantial lag time to onset of therapeutic action. Therefore, there is an urgent public health need to identify more effective, faster acting antidepressant interventions. The current study examined the safety and efficacy of ketamine delivered via an intranasal route as a novel, rapid acting intervention in treatment-resistant depression (TRD).
Methods: Twenty patients with TRD were enrolled in a randomized, double-blind cross-over study of intranasal (IN) ketamine compared to placebo. The primary efficacy outcome measure was change in depression severity 24 hours following ketamine or placebo, measured using the Montgomery-Asberg Depression Rating Scale. Eighteen patients completed all study procedures and constituted the modified intent-to-treat sample.
Results: Subjects evidenced significant improvement in depressive symptoms at 24 hours following ketamine compared to placebo [$t=4.39$, $p<0.001$]. Eight of 18 subjects (44%) met response criteria 24 hours following ketamine administration, compared to 1 of 18 (6%) following placebo ($p=0.033$). Intranasal ketamine was well tolerated with minimal psychotomimetic or dissociative effects. No patient exhibited clinically significant changes in hemodynamic parameters.
Conclusions: This study provides the first controlled evidence for the rapid antidepressant effects of intranasal ketamine. The treatment was associated with minimal adverse effects. If replicated, these findings may lead to novel approaches to the pharmacologic treatment of patients with refractory forms of depression.

Learning Objectives:

- To understand the rationale for ketamine as an antidepressant
- To appreciate different ways that ketamine may be used in the future to treat severe or refractory forms of depression

Literature References:

- Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry. 2013 Oct 1;170(10):1134-42.
- Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013 Aug 15;74(4):250-6.

INDIVIDUAL ABSTRACT:

TREATMENT OF SUICIDALITY WITH NOVEL MECHANISMS

Sanjay Mathew

Baylor College of Medicine

Background: Preliminary evidence suggests intravenous ketamine has rapid effects on suicidal cognition, making it an attractive candidate for depressed patients at imminent risk of suicide. In a randomized controlled trial of ketamine using an anesthetic control condition, we tested ketamine's acute effects on explicit suicidal cognition and on a performance-based index of implicit suicidal cognition (Implicit Association Test; IAT) previously linked to suicidal behavior. Methods: Symptomatic patients with treatment-resistant unipolar major depression (inadequate response to ≥ 3 antidepressants) were assessed using a composite index of explicit suicidal ideation (Beck Scale for Suicidal Ideation, Montgomery-Asberg Rating Scale suicide item, Quick Inventory of Depressive Symptoms suicide item) and the IAT to assess suicidality implicitly. Measures were taken at baseline and 24-hours following a single subanesthetic dose of ketamine (n=36) or midazolam (n=21), an anesthetic medication with no known antidepressant properties. Results: 24-hours post-infusion, explicit suicidal cognition was significantly reduced in the ketamine but not the midazolam group. 53% of ketamine-treated patients scored zero on all three explicit suicide measures at 24-hours, compared with 24% of the midazolam group ($\chi 2=4.6$; $p=.03$). Implicit associations between self- and escape-related words were reduced following ketamine ($p=.01$; $d=.58$) but not midazolam ($p=.68$; $d=.09$). Ketamine-specific decreases in explicit suicidal cognition were largest in patients with elevated suicidal cognition at baseline, and were mediated by decreases in non-suicide-related depressive symptoms. Conclusions: Intravenous ketamine produces rapid reductions in suicidal cognition over and above active placebo. Further study is required to test ketamine's anti-suicidal effects in higher-risk samples, and to examine associated neurobiological mechanisms.

Learning Objectives:

- To review aspects of the assessment of suicide in patients with treatment-resistant depression.
- To discuss new research data for the drug treatment of suicidal ideation.

Literature References:

- Price RB, Nock MT, Charney DS, Mathew SJ (2009): Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 66 (5): 522-526.

• Diazgranados N, Ibrahim L, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA et al (2010): Rapid resolution of suicidal ideation after a single infusion of an NMDA antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 71: 1605-1611.

INDIVIDUAL ABSTRACT:
THE ROLE OF PHERINES FOR RAPID RELIEF OF DEPRESSIVE AND ANXIETY SYMPTOMS

Michael R. Liebowitz
Pherin Pharmaceuticals

The goals of this presentation are twofold. The first is to familiarize the audience with the nasal chemosensory system, which has also been called the vomeronasal system. This system, once considered vestigal in humans, appears to allow application of certain substances called pherines in minute doses to specific areas of the nasal muscosa to have rapid and significant effects on the central nervous system, without having those substances enter into the systemic circulation.. The second goal is to familiarize the audience with recent findings of the efficacy of particular pherines for the rapid relief of anxiety and depressive symptoms in patients with major psychiatric disorders.

The talk will present a brief overview of research on the nasal chemosensory or vomeronasal system and the development of pherines. It will then present data from three trials of particular pherines in patients with social anxiety disorder, generalized anxiety disorder and major depressive disorder.

Data from three clinical trials will be presented showing rapid antianxiety and antidepressant therapeutic effects for pherines. The first is a study of the pherine PH94B in patients with generalized anxiety disorder. Nineteen women with GAD were randomized to double blind treatment with 200 pg PH94B or placebo administered in a one second aerosol pulse directly to nasal chemoreceptors. Ham-A, Covi and clinical electrophysiological measures were administered at baseline and at 30 and 60 minutes post treatment. The second trial involves female patients with generalized social anxiety disorder who were pretreated intranasally with placcebo prior to public speaking and social interaction challenges in the research clinic. Those scoring above a certain level of anxiety during the challenges were brought back for a second set of the same challenges but were randomized to receive pretreatment with either Ph94B in mircrogram doses or placebo delivered intranasally. The third trial was of 30 female patients with major depressive disorder randomized to 8 weeks of twice daily intransal administrations of higher or lower microgram doses of PH 10, another pherine, or placebo.

In the GAD study, substantial effect sizes were seen for PH94B in comparison to placebo on total Ham A score and a number of individual Ham-A items and physiologic measures at 30 minutes. By the 60 minute measurement point all significant improvements had disappeared. In the social anxiety disorder study,. PH94B resulted in significantly greater decreases in both public speaking and social interaction anxiety than did repeat placebo administration. For patients with major depressive disorder, substantial effect sizes in favor of PH0 were seen when comparing Ham D 17 scores between drug and placebo after one as well as after eight weeks of treatment. Side effects in all three trials were benign.

The findings are important for several reasons. The nasal chemosensory system may be a previously unrecognized pathway for the safe and rapid administration of psychotropic drugs. Pherines such as PhH4BB nd PH10 may also represent novel and effective treatment approaches for the rapid relief of significant symptoms of major anxiety and depressive disorders

Learning Objectives:

- To become familiar with the findings of pherines for the rapid treatment of symptoms of social anxiety disorder, generalized anxiety disorder and major depressive disorder.
- To become familiar with the nasal chemosensory or vomeronasal system as a possible means of psychotropic drug delivery.

Literature References:

- Heimberg RG, Liebowitz MR, Hope DA, Schneieir FR, Holt CS, Welkowitz LA, Juster HR, Campeas R, Bruch MA, Cloitre M, Fallon B, and Klein DF: Cogntiive behavioral grouip therapy vis phenelzine for social phobia: 12 week outcome. Archives of General Psychiatry 1998; 55 (12): 1133-1141
- Monti L, Jennings-White C, Berliner DL: The human vomeronasal system: A review. Annals of the New York Academy of Science. Olfaction and Taste II 1998; 855:373-389

NOVEL DEVELOPMENTS IN NON-INVASIVE NEUROSTIMULATION FOR THE TREATMENT OF MOOD DISORDERS

Dan V. Iosifescu
Icahn School of Medicine at Mount Sinai

Current pharmacological treatments for major depressive disorder have significant limitations, primarily related to moderate efficacy and to slow onset of antidepressant effects. Non-invasive device-based neurostimulation (characterized by direct administration of energy to the brain, via magnetic or electrical fields) represents an area of active research in the quest for novel, rapid acting and more efficacious antidepressant treatments. We will review in this presentation data from a study of 233 MDD subjects where deep transcranial magnetic stimulation showed higher decrease in depression severity (Ham-D-21) compared to sham. We will also highlight recent results from a study of 202 MDD subjects, where synchronized TMS (subthreshold magnetic stimulation of the brain delivered at an individual's alpha frequency) was superior to sham in decreasing depressive symptoms (measured by Ham-D-17). Finally, we will discuss an on-going study of low field magnetic stimulation aiming to detect a rapid antidepressant effect with this technology. We will particularly focus on methodological challenges of studies investigating these devices. We will emphasize the strengths and limitations of these treatments and the promise for enhancing both clinical outcomes and our understanding of the biology of depression.

Learning Objectives:

- Discuss the relative differences among several novel methods for non-invasive neurostimulation currently in development.
- Understand the methodological challenges of studies of novel device based treatments in mood disorders.

Literature References:

- Levkovitz Y, Sheer A, Harel EV, Katz LN, Most D, Zangen A, Isserles M. Differential effects of deep TMS of the prefrontal cortex on apathy and depression. Brain Stimul. 2011 Oct;4(4):266-74.

• Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Front Hum Neurosci. 2013; 7:37. doi: 10.3389/fnhum.2013.00037.

WORKSHOP
3:45 PM – 5:45 PM

WORKSHOP OVERVIEW:
PSYCHIATRY AND TECHNOLOGY: A PARTNERSHIP IN PROMOTING MENTAL HEALTH

Holly A. Swartz[1], Victoria E. Cosgrove[2], Mark Matthews[3], David C. Mohr[4], Robert Gibbons[5], Jennifer Silk[6], Ellen Frank[1]
[1]University of Pittsburgh School of Medicine, [2]Stanford University School of Medicine, [3]Cornell University, [4]Northwestern University, [5]University of Chicago, [6]University of Pittsburgh, Department of Psychiatry

Traditional mental health services and interventions have been confined to bricks and mortar systems of delivery. Clinical trials research methodology has typically focused on these face-to-face interventions as well. Although there is tremendous interest in the use of health information technology to move health care into the digital age, clinical trials research is just beginning to catch up with the explosion of technology that is shaping our personal and professional lives. Initial studies of treatments that paired psychiatry with technology sought to "translate" traditional face-to-face interventions into remote applications (e.g., web, telephone) but essentially retained the original constructs of the intervention. Newer studies seek to evaluate completely novel approaches to assessment and care, taking advantage of advances in mobile platforms, sensing capacities of handheld devices, and ubiquity of technology in the lives of both patients and health care professionals. This workshop explores a continuum of applications of technology in behavioral health, with a focus on anticipating future trends. Key presentations will include 1) methods for conducting an international trial of an online intervention for bipolar disorder, 2) development and pilot testing of a smartphone app for monitoring mood and daily routines, 3) overview of the technology development core of Northwestern University Center for Behavioral Intervention Technologies (CBITs; www.cbits.northwestern.edu) with a focus on sensor-based technologies to promote medication adherence, patient monitoring and assessment, 4) the role of computerized adaptive testing (CAT) in improving precision in assessment of behavioral health symptoms, and 5) the use of a smartphone-based ecological momentary intervention to improve skills acquisition CBT. We will invite audience participation to discuss the evolving role of technology in mental health treatments and clinical trials methodology.

Learning Objectives:
• To understand the role of technology in advancing the treatment of psychiatric disorders.
• To examine novel uses of technology to extend or improve upon traditional psychiatric treatments and assessment methods.

INDIVIDUAL ABSTRACT:
MOODSWINGS 2.0 FOR BIPOLAR DISORDER: WWW.MOODSWINGS.NET.AU

Victoria E. Cosgrove
Stanford University School of Medicine

Background: The application of adjunctive psychosocial interventions in bipolar disorder is often limited in real world application due to cost and access constraints. MoodSwings 1.0 was a pilot online self-help program for people with bipolar disorder adapted from a validated group-based face-to-face program. MoodSwings 1.0 compared the online delivery of MoodSwings (interactive tools plus psychoeducation) with psychoeducation alone, using the same platform and both with access to small group moderated discussion boards. Participants diagnosed with bipolar I or II disorder (n = 156) were randomised to either online programs of MoodSwings 1.0 or psychoeducation. Improvement in both groups showed baseline to endpoint reductions in mood symptoms and improvements in quality of life, functionality, and medication adherence. MoodSwings was noted to be superior to psychoeducation in improvement on symptoms of mania at 12 months (p=0.02).
MoodSwings 2.0 was developed in response to these promising findings.
Method: Participants diagnosed with bipolar I,II or NOS will be recruited. MoodSwings 2.0 is a 2-site, 3-arm randomized parallel group stepped design (exposure to moderated peer discussion board only, discussion board only, discussion board plus psychoeducation or discussion board, psychoeduation, and online interactive psychosocial tools. The collaborative sites (Palo Alto, CA, and Melbourne, Australia) will enroll 300 participants internationally. Outcomes will be assessed at quarterly intervals via phone interview with raters blind to group assignment as well as online self report.
Results and discussion: The primary outcome of MoodSwings 2.0 will be the change in depressive symptoms over 12 months, assessing if there is additive benefit to the three components (education, discussion board, and interactive psychosocial tools) on improvement. Exploratory aims include symptoms of elevated mood, health services utilization, evidence of relapse (time to intervention), function, quality of life and medication adherence.
Conclusion and future directions: Experience of the MoodSwings 1.0 trial study suggests that internet-based psychosocial interventions have potential in the management of bipolar disorder. Online enhancements in MoodSwings 2.0, as well as a larger sample size including an attention control (discussion board only arm) may lead to a greater understanding of these interventions as an adjunctive treatment tool.

Learning Objectives:

- Introduce background and rationale for adjunctive online psychosocial interventions for individuals with bipolar disorder.
- Discuss components of the MoodSwings 2.0 program and introduce study methodology from our ongoing, randomized trial to evaluate its efficacy.

Literature References:

- Barak, A., Klein, B., & Proudfoot, J. (2009). Defining Internet-supported therapeutic interventions, Annals of Behavioral Medicine, 38: 4-17.Titov, N. (2007).
- Status of computerized cognitive behavioural therapy for adults. Australian and New Zealand Journal of Psychiatry, 41(2), 95-114.

INDIVIDUAL ABSTRACT:
MOODRHYTHM: PILOT TESTING A SMARTPHONE APP FOR MONITORING MOOD AND DAILY ROUTINES

Mark Matthews

Cornell University
Interpersonal Social Rhythm Therapy (IPSRT) is a behavioral therapy specifically devised to help bipolar patients maintain stable daily rhythms. The work of therapy focuses on the timing of social events in order to establish regular social rhythms to keep patients balanced. To establish and keep track of daily routines, patients use the Social Rhythm Metric (SRM), a 5-item self-report scale that has been clinically validated.
In this presentation, I will talk about the design and piloting of MoodRhythm, an app based on IPSRT, and created to support people with affective illnesses by making it easier to keep track of daily patterns and to increase patient engagement in treatment.
While many approaches have focused predominantly on how patient-collected data could be used in clinical settings, MoodRhythm provides valuable, meaningful and privacy-sensitive feedback to the patient in their daily context, thereby closing the loop and potentially increasing the incentive for self-tracking. In this research, we took a Participatory Design approach to the development of the app, involving individuals with bipolar disorder and clinicians throughout, in order to create a tailored system that is informed by an understanding of clinical practice, and grounded in the day-to-day experience of therapists and patients.
Previous work in mental healthcare has mostly looked at deploying "off the shelf" technologies like SMS, psycho-educational websites and online forums in mental health care settings and provided evidence that these approaches can be effective. Our central contribution is an illustration of how, when working with patients with bipolar disorder, and in mental health care generally, technology design may incorporate considerations of the low-level characteristics of the illness, the therapeutic approach, and the lived experience of people with the illness. Such an approach has the potential to greater patient engagement and ultimately to improved outcomes.

Learning Objectives:
- Gain an overview of the currently available technologies to support the management and treatment of bipolar disorder.
- Learn novel ways that technology can support the long-term management of bipolar disorder.

Literature References:
- Frank, E., Kupfer, D. J., Thase, M. E., Mallinger, A. G., Swartz, H., Fagiolini, A. M., Grochocinski, V., Houck, P., Scott, J., Thompson, W., & Monk, T. (2005).
- Two year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Archives of General Psychiatry, 62,996-1004.
- Monk, T.K., J.F. Flaherty, E. Frank, and K. Hoskinson, The social rhythm metric: an instrument to quantify the daily rhythms of life. Journal of Nervous and Mental Disease, 1990.

INDIVIDUAL ABSTRACT:
COMPUTERIZED ADAPTIVE TESTING (CAT) AND THE FUTURE OF PSYCHIATRIC MEASUREMENT
Robert Gibbons
University of Chicago
Mental health measurement has been based primarily on subjective judgment and classical test theory. Typically, impairment level is determined by a total score, requiring that all respondents be administered the same items. An alternative to full scale administration is adaptive testing in which different individuals may receive different scale items that are targeted to their specific

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

Learning Objectives:
- Learn about IRT-based computerized adaptive testing.
- Discuss improved mental health measurement.

Literature References:

- Gibbons RD, et al. The CAT-DI: A computerized adaptive test for depression. Archives of General Psychiatry, 2012;69:1104-1112.
- Gibbons R.D., Hooker, G., Finkelman, M.D., Weiss, D.J., Pilkonis, P.A., Frank, E., Moore, T. Kupfer, D.J. The CAD-MDD: A computerized adaptive diagnostic screening tool for depression.J of Clinical Psychiatry, e-pub.

INDIVIDUAL ABSTRACT:
USING SMARTPHONES TO ENHANCE SKILL ACQUISITION AND UTILIZATION IN CBT FOR CHILD ANXIETY

Jennifer Silk
University of Pittsburgh

Psychologists have long assessed emotions in real life settings using Ecological Momentary Assessment (EMA). CBT therapists and research findings have also emphasized the importance

of "homework" in generalizing skills beyond the clinic. Advances in mobile health (mHealth) technologies provide an opportunity to merge these methods through the development of Ecological Momentary Interventions that are delivered to people during their everyday lives. mHealth technologies have the potential to improve youth engagement in treatment and provide opportunities to practice CBT skills in vivo. These approaches might be particularly fruitful in working with youth, given their comfort and engagement with technology. We developed an adjunctive intervention called SmartCAT (Smartphone-Enhanced Child Anxiety Treatment), consisting of a smartphone application (app) for youth and an integrated clinician portal. The app contains: (1) an "in vivo" skills coach that cues the participant to use CBT skills during real-world emotional experiences, (2) a media library that includes treatment-related documents, videos, and mp3 files, (3) a digital reward bank, and (4) a clinician-patient messaging interface. Therapists use a secure web-based portal connected to the app to receive or send messages and files, manage child rewards, and view data and figures summarizing skills coach entries. SmartCAT was tested with 15 anxious youth ages 9-14; (M=11.94, SD=1.77) receiving either a brief 8 session version of CBT (N=8) or 14-16 session CBT (N=7). 13 youth completed all sessions and 2 cases (both full CBT) are still active. Among youth receiving a full course of CBT + SmartCAT, 60% were classified as treatment responders based on independent evaluator (IE)-rated CGI-I score and remission of primary anxiety diagnosis at post-treatment. This was higher than treatment response rates for the group that received brief treatment (CGI-I response rate = 50%). Paired t-tests on continuous treatment outcomes indicated that youth showed significant improvements from pre- to post-treatment on parent, child, and IE-rated anxiety severity (all p's <.05), regardless of whether they received brief or full treatment. Participants rated the app as easy to use (M=2.1 [SD=.47] on a 1-7 scale, with 1= "easy"). Entries took an average of 3.05 minutes to complete (SD=2.39 min) and children completed an average of 5.36 skills coach entries per session (SD=3.88). Regardless of receiving brief or full CBT, treatment satisfaction ratings were high (M=3.46 [SD=.66] on a 1-4 scale). Findings provide preliminary support for the feasibility and acceptability of integrating the SmartCAT intervention with CBT for child anxiety. We will discuss plans to integrate interactive gaming and GPS-based context sensing into the app to further increase patient engagement and treatment personalization, and to conduct a randomized clinical trial to test the efficacy of the program compared to standard CBT.

Learning Objectives:

- To learn how Ecological Momentary Intervention can be used to improve skill acquisition and utilization in psychosocial treatments.
- To learn specific strategies for incorporating smartphone technology into CBT for child anxiety.

Literature References:

- Heron, K. E., & Smyth, J. M. (2010). Ecological momentary interventions: Incorporating mobile technology into psychosocial and health behavior treatments. British Journal of Health Psychology, 15(1), 1-39.
- Kendall, P. C., Settipani, C. A., & Cummings, C. M. (2012). No need to worry: The promising future of child anxiety research. Journal of Clinical Child and Adolescent Psychology, 41(1), 103-115.