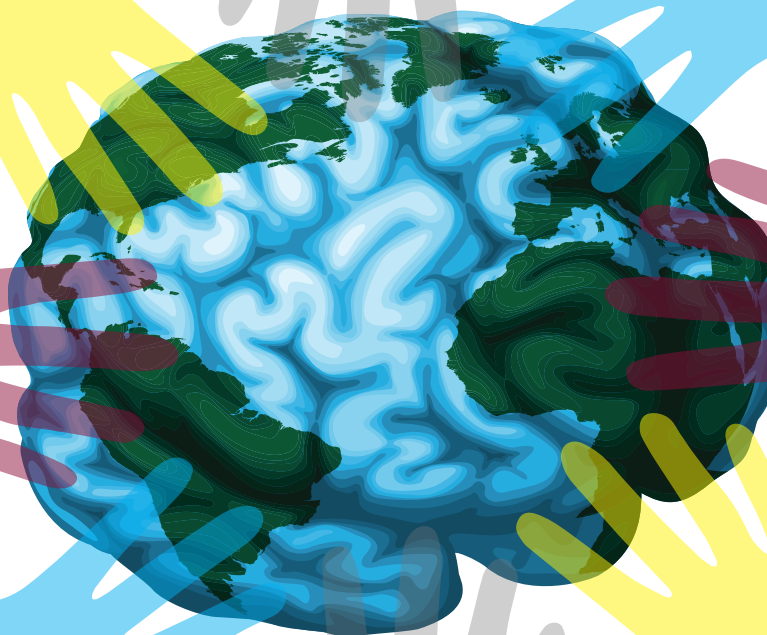


ABSTRACT BOOK

ASCP ANNUAL MEETING
LOEWS MIAMI BEACH HOTEL
MAY 29–JUNE 2, 2017

SERVING THE NEEDS



OF THE DIVERSE POPULATION



ASCP
AMERICAN SOCIETY OF
CLINICAL PSYCHOPHARMACOLOGY

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Monday, May 29, 2017

12:00 p.m. - 1:50 p.m.

Latin American Symposium*

LATIN AMERICAN SYMPOSIUM

Francisco Moreno, University of Arizona

Overall Abstract: Many factors affect mental illness expression, access to care, quality of care, and treatment response. Latinos represent highly heterogeneous groups including individuals from multiple nationalities, races, languages, socioeconomic and literacy statuses, life strategies, and cultural perceptions and health, and health care. This Latin American Symposium represents a collaboration of academia and industry, national and international professional societies, and covers topics of interest to American Latino communities, Latin American countries, and the field of Clinical Psychopharmacology in general. A distinguished group of speakers will cover impactful topics including: description of social determinants of mental health, and outcomes relevant to Latino communities; Culturally tailored wellness interventions in U.S. Latinos in prevention of mental health conditions; Prevalence of Bipolar Disorder in Emergency Department encounters in Latin American countries, including symptoms resulting in care seeking, and associated comorbidities; Identification of new targets in the search for innovative therapeutic opportunities in mood disorders; Posttraumatic Stress Disorder and Gender in Ecuador; Updates in PTSD clinical psychopharmacology; and Novel agents for the treatment of Obsessive Compulsive Disorder.

Learning Objectives:

- To understand factors that are relevant to psychiatric expression and treatment of Latino populations in the US and countries of origin.
- To review novel prevention and treatment strategies for ordinary and difficult to treat mood and anxiety disorders.

OVERCOMING LATINO MENTAL HEALTH DISPARITIES VIA HEALTH PROMOTION

Daniel Jimenez, University of Miami

Individual Abstract: The combination of high prevalence of common mental disorders, low mental health service use, differing mental health beliefs, and high stigma illustrate the need to create culturally appropriate interventions for older racial/ethnic minority adults. Available treatments are difficult to access and only partially satisfactory in reducing symptom burden, sustaining remission, and averting years lived with disability. These factors underscore the need for interventions focused on prevention that are both effective and scalable. One promising approach is the use of lay community health workers (CHWs). The use of CHWs is an important means of task shifting to enable more efficient utilization of scarce mental health resources. Latino older adults are an important and appropriate group in whom to develop and test innovative, culturally adapted approaches for prevention of common mental

**of special interest to clinicians*

disorders. They are the largest and fastest growing segment of the older adult population. Moreover, high prevalence of common mental disorders combined with mental health service use disparities makes older Latinos a high-risk population for whom scalable preventive interventions could have great public health impact. In addition, older Latinos are at increased risk for diabetes, obesity, reduced physical activity, and mortality. Cultural beliefs about the causes of mental illness and stigma about help seeking may further contribute to Latinos' limited access and low utilization of mental health care. The design of an exploratory, randomized controlled pilot trial testing the feasibility of a health promotion intervention, led by a CHW, to prevent depression and anxiety in at-risk older Latinos will be discussed. The primary outcomes are preemption of incident and recurrent major depression, generalized anxiety, or social phobia and reduction in depression and anxiety symptom severity. Secondary outcomes include changes in physical functioning, sedentary behaviors, social engagement, and self-efficacy. The results of this study could have implications for other high risk, highly disadvantaged populations. The development of a health promotion intervention designed to prevent common mental disorders could be a means of addressing multiple disparities (e.g. mental health outcomes, mental health service use, stigma) among other racial/ethnic minority elderly.

Learning Objectives:

- At the end of this session, participants will know the Institute of Medicine's definition of disparities.
- At the end of this session, participants will learn the role of health promotion in reducing mental health disparities among Latino older adults.

Literature References:

- Jimenez DE, Alegría M, Chen C-N, et al. Prevalence of psychiatric illness among ethnic minority older adults. *J Am Geriatr Soc.* 2010; 58: 256-64.
- Jimenez, D. E., Cook, B. L. Bartels, S. J., & Alegría, M. (2013). Disparities in Mental Health Service Use among Ethnic Minority Adults. *Journal of the American Geriatrics Society*, 61, 18-25.

IDENTIFYING PATIENTS WITH BIPOLAR DISORDERS IN EMERGENCY DEPARTMENTS IN LATIN-AMERICAN COUNTRIES: COMORBIDITY AND LEADING SYMPTOMS

Ruby Castilla Puentes, Johnson and Johnson

Individual Abstract: Objectives: This study estimated the prevalence of bipolar disorder (BPD) among emergency department (ED) patients in Latin America. Comorbidity and Leading Symptoms were also explored.

Methods: To identify patients with BPD, a combination of DSM IV- criteria interview and a questionnaire screen including the Mood Disorder Questionnaire (MDQ) was used. Data from consecutive 1,505 patients from hospitals in Argentina, Brazil, Chile, Colombia, and Mexico was analyzed to calculate prevalence and to describe the demographic, comorbidity and leading symptoms differences between BPD and non-BPD patients.

Results: The prevalence of BPD in this population was 5.2% (95% CI= 4.5 to 6.9). The mean age was 37 years, with response rate of 83.0%. Compared to non-BPD patients, BPD patients were more likely to report a diagnosis of asthma (16.7% vs. 9%), thyroid problems (12.8% vs. 5.8%), seizures (23.1% vs. 3.0%), and to suffer of obesity (39.7% vs. 26.9%, all $p \leq 0.05$).

BPD patients versus those without BPD were also differentiated in their psychiatric comorbidity as follows: higher rate of alcohol abuse (30.8% vs. 10.0%), attention deficit hyperactivity disorders (50.0% vs. 12.0%), depression (81.6% vs. 45.7%), obsessive compulsive disorder (20.1% vs. 3.0%), panic disorders (23.1% vs. 12.3%), phobic disorders (11.2% vs. 3.1%), and any anxiety disorder (82.1% vs. 41.8%). Compared to non-BPD, suicidal plans and attempts were also significantly higher in the bipolar group (11.5% vs. 2.8% and 10.3% vs. 1.8% respectively). Multivariate analysis identified ADHD, depression, alcohol abuse, anxiety disorder and last month suicide plans and attempts to be independently associated with BPD. Leading symptoms identified in patients with BPD include: irritability, anxiety, pressured speech, euphoria, those with suicidal tendencies, or involved in risky behaviors, alcohol abuse, dependence or history of mental health hospitalization in the past 12 months.

Conclusion: Our study supports that BPD is prevalent in ED in Latin-American countries and that comorbidity is the rule, not the exception. Also provides further evidence that the burden of chronic medical conditions in persons with BP is substantial. Patients presenting at ED with leading symptoms (e.g. irritability, anxiety, pressured speech, euphoria, etc.) must be assessed for comorbid BPD.

Learning Objectives:

- Identify symptoms.
- Identify correlates of BPD in Emergency Department patients from Latin American countries.

Literature References:

- Callaghan, P., Eales, S., Leigh, L., Smith, A., & Nichols, J. (2001). Characteristics of an Accident and Emergency liaison mental health service in East London. *J Adv Nurs*, 35(6), 812-818
- Bacaner, N., Kinney, T. A., Biros, M., Bochert, S., & Casuto, N. (2002). The Relationship among depressive and alcoholic symptoms and aggressive behavior in adult male emergency department patients. *Acad Emerg Med*, 9(2), 120-129.

EFFECT OF A NOVEL NMDA RECEPTOR MODULATOR, RAPASTINEL (FORMERLY GLYX-13) IN OCD: PROOF-OF-CONCEPT

Carolyn Rodriquez, Stanford University

Individual Abstract: Background: A single intravenous dose of ketamine produces robust and rapid anti-obsessional effects in obsessive-compulsive disorder (OCD), but ketamine's side effects, including dissociation and nausea, may limit clinical use. Rapastinel (formerly GLYX-13), an NMDAR modulator, has shown rapid anti-depressant activity without ketamine-like side effects, and may be a new therapeutic strategy for OCD. We conducted the first study of the efficacy and tolerability of rapastinel administration in OCD.

Methods: Seven unmedicated OCD outpatients (aged 18-55) with at least moderate symptoms (Y-BOCS score ≥ 16) received a single 3-5 minute IV push of rapastinel (dose=10 mg/kg). At baseline, 90, and 230 minutes post-infusion, patients self-rated the severity of their obsessions and compulsions (YBOC Challenge Scale [YBOCCS]), anxiety (Beck Anxiety Inventory [BAI]), and depression (Beck Depression Inventory [BDI]). At baseline and one week post-infusion, an independent evaluator, blind to study design, evaluated

patients using the Y-BOCS, which appraises obsessive and compulsive symptoms over the prior week, and patients self-rated anxiety (BAI) and depression (BDI). Outcomes were analyzed using a non-parametric Wilcoxon signed-rank matched-pairs test ($\alpha = .05$, two-tailed) without adjustment for multiple comparisons given the exploratory nature of this study.

Results: Compared to baseline, YBOCCS, BAI, and BDI scores were significantly lower at 90 and 230 minutes post-infusion (all p values $< .05$; the percentage decrease in YBOCCS from baseline to 230 minutes post infusion was 46.4%). OCD severity, as measured by the Y-BOCS, was not significantly decreased ($p = .20$) from baseline to one week post-infusion, nor was BDI ($p = .20$), although BAI was significantly decreased ($p = .02$). No patient met the a priori treatment response criterion ($\geq 35\%$ Y-BOCS reduction) at one week post-infusion. Participants did not report adverse events.

Conclusions: The findings suggest that rapastinel is well tolerated in unmedicated OCD patients, as it is in patients with depression. Specifically, no patients reported psychotomimetic or dissociative adverse events, unlike ketamine in prior studies. In this small open-label sample, rapastinel demonstrated acute efficacy on obsessions and compulsions, anxiety and depression. Future studies will examine multiple doses of rapastinel as a means to increase duration of response.

Learning Objectives:

- To understand the phenomenology and current treatments for OCD.
- To review experimental treatment development strategies for OCD.

Literature References:

- Rodriguez, C.I., Kegles, L.S., Levinson, A., Feng, T., Marcus, S., Flood, P., & Simpson, H.B. (2013). Randomized Controlled Crossover Trial of Ketamine in OCD: Proof of Concept. *Neuropsychopharmacology*, 38(12), 2475-83.
- Rodriguez, C.I., Zwerling, M., Kalanthroff, E., Shen, H., Filippou, M., Jo, B., Simpson, H.B., Burch, R., Moskal, J.R. Effect of a Novel NMDA Receptor Modulator, Rapastinel (formerly GLYX-13) in OCD: (2016). A Pilot Study. *American Journal of Psychiatry*. 173:12; 1239-1240.

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

Latin American Symposium*

ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF PTSD

Gerardo Villarreal, University of New Mexico

Individual Abstract: Antidepressants are considered first line treatment for PTSD. They have modest benefit, particularly for affective reactivity. Interestingly, only 2 medications are FDA-approved for the treatment of PTSD: Paroxetine and sertraline, although all the selective serotonin reuptake inhibitors (SSRI's) and venlafaxine are likely helpful. The psychopharmacological treatment of chronic and cases can be challenging. The Veteran Affairs/Department of Defense PTSD treatment guidelines recommend prazosin and atypical antipsychotics as adjunct medications. However, a large randomized trial of risperidone in treatment-resistant PTSD did not show it was superior to placebo for global PTSD symptoms.

A post-hoc analysis of the data did show improvement in re-experiencing in and hyperarousal clusters. A double-blind placebo controlled trial of quetiapine as single agent revealed it was effective for global PTSD symptoms, re-experiencing and hyperarousal clusters as well as depression and anxiety. A post-hoc analysis revealed it was effective for insomnia. The main limitation of atypical antipsychotics is metabolic side effects, for that reason, they need to be used in treatment-resistant and severe cases. Weight gain and metabolic measures need to be monitored closely.

Learning Objectives:

- Understand the effects of serotonin reuptake inhibitors in PTSD.
- Review research findings of atypical antipsychotics in PTSD.

Literature References:

- Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, Horney RA, Huang GD, Stock C: Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA*, 2011; 306:493-502
- Villarreal G, Hamner MB, Cañive JM, Robert S, Calais LA, Durklaski V, Zhai Z Clifford Q: Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial. *American Journal of Psychiatry*, 173:1205-1212, 2016

PTSD AND GENDER VIOLENCE: ECUADOR EXPERIENCE

Victoria Valdez, International Federation of Societies of Biological Psychiatry

Individual Abstract: Objectives: The aim of this study is to determine the incidence of traumatic events in Ecuadorian women exposed to domestic violence, community gender violence and their relationship with PTSD.

Methods: We applied a transversal descriptive study to the INEC data base (Ecuadorian National Institute of Statistics and Census). The INEC recruited Ecuadorian women from 15 years old and ahead, the surveys were focused on this population: 36,328 Ecuadorian women. 18,800 rural and urban housings were selected all over the country, 24 provinces. Date of the survey: November 16 – December 15 of 2011. A, G and H were taken as guidelines from the DSM V (Diagnostic and Statistical Manual of Mental Disorders) to determine Traumatic Events.

Results: The average age of the sample was 28 years old. The standard deviation was 21. 15-25: 14,265 (21.6%), 25-35: 9,324 (14.1%), 35-45: 8,132 (12.3%), 45-55: 6,283 (9.5%), 55-65: 4,302 (6.5%), >65: 23,745 (35.9%). Prevalence of traumatic events (DSM V) 4.6%.

Women experienced violence: 60.6 %. 61.4% urban, 58% rural. Types of abuse: psychological: 53.9%, physical: 38.0; sexual: 25.7%, financial: 35.3%. Domestic violence 76.0% y community gender violence (relatives, job): 24.0%.

Conclusion: Domestic violence revealed a 60.6% rate. Furthermore, in this study we highlighted the issue of women facing an important index of violence during their daily life activities, interaction with their relatives, Jobs. Psychological violence is the highest type of violence, more in urban areas, than in rural areas. Sexual violence attracted our attention with an important index of suicide attempts. In summary, we concluded that acute traumatic events may predispose women to develop PTSD. The prevalence of traumatic events must be an alert to Mental Health Organizations, not only in Ecuador but also in Latin-America.

Learning Objectives:

- At the end of the lecture the audience should be able to determine the relationship between posttraumatic stress disorder and gender violence.
- The audience can recognize the different types of gender violence.

Literature References:

- Diagnostic and statistical manual of mental disorders. dsm v
- Current concepts- iposttraumatic stress disorder. yehuda 2002
- Global mental action. intimate partner violence and mental health; domestic violence and mental health: a cross sectional survey of women seeking help from domestic violence support services. g ferrari. august 2014
- The national center for posttraumatic stress disorder. sex differences in risk of PTSD. d f. tolin 2007
- Psychosocial intervention. miedo, conformidad y silencio. la violencia en las relaciones de pareja en areas rurales de ecuador. s boira. univ zaragoza. 2015
- Psychotraumatology. adult experience of mental health outcomes as a result of intimate partner violence victimisation: a system overview. s. lagdon. univ. ulster 2014
- La evaluacion del trastorno por estrés posttraumatico: aproximacion a las propiedades psicometricas de las escala de tauma de davidson. a villafane. univ cordoba. 2003
- Sex differences in PTSD. d christiansen. aarhus univ.
- Prevalence and characteristics of sexual violence, stalking and intimate partner violence victimization- national intimate partner and sexual violence survey, united states. m.j. breiding. 2011
- Perfil psicopatologico e intervencion terapeutica con los agresores contra la pareja. e. echeburua. uni del pais vasco, san sebastian. 2010
- Psicothermia. diagnostic concordance of dsm- iv and dsm 5 posttraumatic stress disorder in a clinical sample. m crespo. uni complutense. 2015
- Intimate partner violence. p. f cronholm. Univ Pennsylvania 2011
- Violencia contra la mujer en la pareja y consecuencias en la salud fisica y psiquica. i. ruiz perz. red de investigacion de salud y genero. granada. 2004

PHARMACOLOGICAL UPDATES IN MOOD DISORDERS

Rodrigo Machado-Vieira, UTHSC at Houston, School of Medicine

Individual Abstract: Recent developments in mood disorders research identified new targets in the search of innovative therapeutic approaches and are providing new and exciting opportunities. This presentation will evaluate current and new therapeutic approaches for mood disorders and associated biomarkers of response relevant for CNS drug development and personalized treatment. These targets may be of substantial interest in defining future directions in drug development, as well as in developing the next generation of therapeutic agents for the treatment of mood disorders. Emphasis on studies developed in our lab with lithium, new mood stabilizers and glutamate modulators will be given, highlighting new concepts, tools and clinical utility of these agents in mood disorders and beyond. Overall,

further study of these and similar agents may lead to a better understanding of relevant and clinically useful drug targets in the treatment of these devastating illnesses.

Learning Objectives:

- The participant will understand the rationale for developing and clinical utility of standard and new modulators for mood disorders beyond the monoaminergic system.
- The participant will understand what are the mood stabilizers being developed for bipolar disorder.
- To understand predictors of response and surrogate outcomes in depression and mania associated with lithium and other neuroprotective agents in mood disorders.

Literature References:

- Machado-Vieira R, Henter ID, Zarate CA Jr. New targets for rapid antidepressant action. *Prog Neurobiol*, 2015 [Epub ahead of print]. PubMed:26724279.
- Machado-Vieira R, Otaduy MC, Zanetti MV, De Sousa RT, Dias VV, Leite CC, Forlenza OV, Busatto GF, Soares JC, Gattaz WF. A Selective Association between Central and Peripheral Lithium Levels in Remitters in Bipolar Depression: A 3T-(7) Li Magnetic Resonance Spectroscopy Study. *Acta Psychiatr Scand*. 2015

Tuesday, May 30, 2017

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

Tuesday Morning Panel Sessions

IMPLEMENTING MEASUREMENT-BASED CARE IN CLINICAL PRACTICE*

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

Overall Abstract: Psychiatric and behavioral illness are common; however, it is estimated that fewer than half of people receive guideline-concordant treatment. Experts and advocates in mental health care have called for implementation of systems for improving the diagnosis and treatment based on use of validated patient-rated scales, called measurement-based care. In this panel, we will present the concept and examples of ways to implement measurement-based care. Measurement-based care (MBC) entails the acquisition and use of clinical information typically provided by patients but also often provided by caregivers/partners, that informs the full range of clinical tasks (e.g. screening/early detection; establishing a differential diagnosis; treatment selection, optimization, and avoidance; side effect of minimization; prognostication; and clinical management planning) at the individual patient level. This presentation provides the conceptual basis for and discusses the potential value and costs of MBC in advancing clinical decision-making. The implications of an MBC emphasis for the design and reporting of clinical studies, for provider-patient partnerships and health care system management will be discussed. The design and implementation of the Penn State Clinical Assessment and Rating Evaluation System (PCARES) will be presented. Our goal was to create a system that would provide clinicians and patients with data to enhance the clinical encounter. It was hypothesized that collecting assessment and treatment information across patients and clinicians would result in more efficient and effective care

**of special interest to clinicians*

across patients. Data from the first year of the program will be presented. Applying a measurement based care approach to helping children and adolescents presents unique challenges, such as the need to collect developmentally relevant information and the need to collect information from multiple informants. This presentation will describe how measurement based care is being pursued in the youth arm of the Penn State Clinical Assessment and Rating Evaluation System (PCARES). The measurement model will be described, followed by a description of how that measurement model is being operationalized. Preliminary data on implementing PCARES-youth will also be presented, with a brief discussion of advantages and challenges that have emerged in pursuing this system. The National Network of Depression Centers (NNDC) has developed and launched the Mood Outcomes Program a major NNDC initiative designed to create a common learning health system for patients with mood disorders. Patients receiving treatment at the 23 NNDC Depression Centers and affiliated clinics are being enrolled with the goal of including 25,000 patients over 5 years. The Mood Outcomes program collects patient rated outcomes in a standardized electronic format and feeds the information graphically back to their clinicians in real time. The goals of the program are to 1) promote measurement based care tracking the PHQ-9, GAD-7, C-SSRS screener and the Altman Mania Rating Scale at each visit 2) facilitate quality improvement at the clinic and population level 3) support ongoing research and 4) provide decision making tools for clinicians. We will report baseline demographic, diagnostic and clinical characteristics for over 3,000 patients as well as response and remission outcomes. How the program is being used for quality improvement initiatives and facilitating NNDC research studies will also be discussed.

Learning Objectives:

- Participants will be able to define measurement-based care.
- Participants will be able to list benefits and challenges of implementing measurement-based care.

MEASUREMENT-BASED CARE: A PLATFORM FOR PERSONALIZED CLINICAL DECISION-MAKING*

Augustus Rush, National University of Singapore

Individual Abstract: Measurement-based care (MBC) entails the acquisition and use of clinical information typically provided by patients but also often provided by caregivers/partners, that informs the full range of clinical tasks (e.g. screening/early detection; establishing a differential diagnosis; treatment selection, optimization, and avoidance; side effect of minimization; prognostication; and clinical management planning) at the individual patient level. This clinical information also establishes a platform upon which laboratory-based measures are likely to be placed to further advance these clinical tasks. This presentation provides the conceptual basis for and discusses the potential value and costs of MBC in advancing clinical decision-making. For example, an MBC approach to diagnosis entails a systematic interview to establish the signs, symptoms, and course of illness. MBC also effectively adapts and tailors treatments to individual patients to enhance efficacy, minimize side effect burden, and achieve optimal dosing. MBC may be used to identify person-level care indicators, for example, to estimate an individual's likelihood of relapse following achievement of response or remission, that in turn can tailor the intensity of follow-up visits to specific patients. MBC may generate metrics to estimate for individuals, the presence of DVTs, serotonin syndrome, bipolar disorder or the early detection of very likely treatment non-response. The implications of an MBC emphasis for the design and

reporting of clinical studies, for provider-patient partnerships and health care system management will be discussed.

Learning Objectives:

- Identify 4 core clinical tasks that are performed better with measurement based care (MBC).
- Specify 4 tools in the public domain that can be used for MBC in psychiatry.

Literature References:

- Tong Guo, etal. Measurement based Care vs Standard Care for Major Depression. 2015 Am J Psych. 172:1004-1013, 2015.
- Rush A J etal Medication treatment for the Severely and Persistently Mentally Ill: The Texas Medication Algorithm Project 1999.J Clin Psychiatry 60:284-291

DESIGN AND IMPLEMENTATION OF THE PCARES PROGRAM: PENN STATE CLINICAL ASSESSMENT AND RATING EVALUATION SYSTEM*

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

Individual Abstract: The design and implementation of the Penn State Clinical Assessment and Rating Evaluation System (PCARES) will be presented. This system was developed to systematically gather patient-report symptoms in a trans-diagnostic fashion at evaluation, and follow outcome throughout treatment with validated measures. We will present the decisions made to design and implement the program. We chose to implement screening for adults of a broad set of symptom areas (mood, anxiety, psychosis), transdiagnostic symptoms (anger, aggression, sleep, memory problems), behaviors (disruptive behaviors, eating, substance use, antisocial actions), and a measurement of functioning. Our goal was to create a system that would provide clinicians and patients with data to enhance the clinical encounter. Secondary goals include using the data for clinical quality programs and for research purposes. It was hypothesized that collecting assessment and treatment information across patients and clinicians would result in more efficient and effective care across patients. Data from the first year of the program will be presented.

Learning Objectives:

- The learner will be able to describe pros and cons of patient-rated outcomes.
- The learner will be able to describe the aims of the PCARES program.

Literature References:

- Rush AJ. Isn't It About Time to Employ Measurement-Based Care in Practice? Am J Psychiatry. 2015;172:934-936.
- Harding KJ, Rush AJ, Arbuckle M, Trivedi MH, Pincus HA. Measurement-based care in psychiatric practice: a policy framework for implementation. J Clin Psychiatry. 2011;72:1136-1143.

PENN STATE CLINICAL ASSESSMENT AND RATING EVALUATION SYSTEM FOR YOUTH*

Daniel Waschbusch, Penn State Milton S. Hershey Medical Center

Individual Abstract: Applying a measurement based care approach to helping children and adolescents presents unique challenges, such as the need to collect developmentally relevant information and the need to collect information from multiple informants. This presentation will describe how measurement based care is being pursued in the youth arm of the Penn State Clinical Assessment and Rating Evaluation System (PCARES). The measurement model will be described, followed by a description of how that measurement model is being operationalized. Preliminary data on implementing PCARES-youth will also be presented, with a brief discussion of advantages and challenges that have emerged in pursuing this system.

Learning Objectives:

- Learn the aims and procedures used in PCARES-youth.
- Learn about the challenges and decisions unique to measurement based care in youth.

Literature References:

- Fortney JC, Unutzer J, Wrenn G, Pyne JM, Smith GR, Schoenbaum M, Harbin HT. A tipping point for measurement-based care. *Psychiatric Services*. 2016. Advanced online publication.
- Youngstrom EA, Van Meter A. Empirically supported assessment of children and adolescents. 2016. Advanced online publication.

MOOD OUTCOMES PROGRAM: NATIONAL NETWORK OF DEPRESSION CENTERS*

David Katzelnick, Mayo Clinic

Individual Abstract: The National Network of Depression Centers (NNDC) has developed and launched the Mood Outcomes Program a major NNDC initiative designed to create a common learning health system for patients with mood disorders. Patients receiving treatment at the 23 NNDC Depression Centers and affiliated clinics are being enrolled with the goal of including 25,000 patients over 5 years. The Mood Outcomes program collects patient rated outcomes in a standardized electronic format and feeds the information graphically back to their clinicians in real time. The goals of the program are to 1) promote measurement based care tracking the PHQ-9, GAD-7, C-SSRS screener and the Altman Mania Rating Scale at each visit 2) facilitate quality improvement at the clinic and population level 3) support ongoing research and 4) provide decision making tools for clinicians. We will report baseline demographic, diagnostic and clinical characteristics for over 3,000 patients as well as response and remission outcomes. How the program is being used for quality improvement initiatives and facilitating NNDC research studies will also be discussed.

Learning Objectives:

- Describe the goals of a Learning Healthcare System.
- Understand how a system can simultaneously deliver individual patient level measurement based care and be used for clinical research.

Literature References:

- Rush AJ, *Am J Psychiatry*. Isn't It About Time to Employ Measurement-Based Care in Practice? 2015 Oct;172(10):934-6. doi: 10.1176/appi.ajp.2015.15070928. Epub 2015 Aug 28.

- Charles P. Friedman, Adam K. Wong, David Blumenthal, Achieving a Nationwide Learning Health System. *Science Translational Medicine* 10 Nov 2010: Vol. 2, Issue 57, DOI: 10.1126/scitranslmed.3001456 Rush AJ1.

THE ROLE OF MODULATORS OF THE OPIOID SYSTEM IN THE TREATMENT OF NEUROPSYCHIATRIC ILLNESSES*

Maurizio Fava, Massachusetts General Hospital

Overall Abstract: Endogenous opioids appear to have important roles in the regulation and modulation of brain functioning. Opioid receptors are densely distributed in cortical regions implicated in the response to stressors, as well as the regulation and/or integration of emotionally significant stimuli, including the rostral anterior cingulate and prefrontal cortex. In addition, the opioid system has a prominent sub-cortical regulatory role in the striatopallidal pathway (nucleus accumbens and ventral pallidum) and associated circuits (amygdala, thalamus, insular cortex), which are also involved in the processing of stressful stimuli and regulation of mood. In this panel, Dr. Foster will review in her presentation the preclinical evidence for the potential therapeutic effects of opioid modulators in neuropsychiatric disorders. Dr. Ehrich will present the data relevant to the recently completed development program focused on studying the role of the opioid modulating buprenorphine/samidorphan combination in the treatment of depressed patient with inadequate response to antidepressant therapies. Dr. Marcus will discuss the clinical development program of a kappa antagonist in psychiatric disorders. Finally, Dr. Keck will present the clinical evidence for the potential therapeutic efficacy of tramadol and other opioid agents in the treatment of refractory OCD. Dr. Alpert will serve as the discussant for the panel, providing a commentary to the four presentations.

Learning Objectives:

- The participants will become familiar with the neuro modulating effects of the opioid system.
- The participants will become familiar with the evidence for possible therapeutic indications of opioid modulation in psychiatry.

PRECLINICAL EVIDENCE FOR POTENTIAL THERAPEUTIC EFFECTS OF OPIOID MODULATORS IN NEUROPSYCHIATRIC CONDITIONS*

Simmie Foster, Massachusetts General Hospital & Harvard Medical School

Individual Abstract: This presentation reviews preclinical studies on opioid modulators as potential treatments for neuropsychiatric disease ranging from treatment-resistant depression to post-traumatic stress disorder. Studies on kappa and nociceptin opioid receptor antagonists will be highlighted, as these classes of modulators have shown particular promise as antidepressants and anxiolytics in rodent behavioral assays. New avenues of preclinical research will be discussed, including elucidating cross-talk between opioid receptors and the glutamatergic system, interrogating the interaction of the opioid system with other systems such as immune and endocrine, and defining neural circuits that are regulated by opioid modulators. Challenges to translating potential new opioid modulators from the lab to the clinic will also be discussed. For example, there are species differences in the distribution and localization of opioid receptors in the brain, leading to different effects in rodents and humans. There may even be differences in response between different strains of rats. With

these caveats in mind, advantages of mouse and rat models include the ability to use genetic, optogenetic, and pharmacological tools to dissect the molecular and cellular mechanisms of opioid signaling in neuropsychiatric disease. Understanding these mechanisms may lead to development of opioid modulators with less off-target effects and increased effectiveness in neuropsychiatric disease.

Learning Objectives:

- Describe preclinical evidence for opioid treatment of neuropsychiatric disease.
- Describe limitations and utility of preclinical models for opioid research.

Literature References:

- Zaveri NT: Nociceptin Opioid Receptor (NOP) as a Therapeutic Target: Progress in Translation from Preclinical Research to Clinical Utility. *J. Med. Chem.* 2016; 59:7011–7028[cited 2016 Nov 17] Available from: <http://pubs.acs.org/doi/abs/10.1021/acs.jmedchem.5b01499>
- Dogra S, Kumar A, Umrao D, Sahasrabudhe AA, Yadav PN: Chronic Kappa opioid receptor activation modulates NR2B: Implication in treatment resistant depression. *Sci. Rep.* 2016; 6:33401[cited 2016 Nov 17] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27634008>

THE ROLE OF BUPRENORPHINE/SAMIDORPHAN IN THE TREATMENT OF RESISTANT DEPRESSION

Elliot Ehrich, Alkermes, PLC

Individual Abstract: There is growing preclinical and clinical evidence, including human PET imaging studies, indicating that major depressive disorder (MDD) is associated with dysregulation of endogenous μ and κ opioid neurotransmitters including the endorphins and dynorphins. The routine clinical use of opioid agonists to treat MDD and related mood disorders is not practical due to the risk for abuse and addiction. In an effort to therapeutically address endogenous opioid dysregulation in MDD while avoiding abuse and addiction, we studied a combination of buprenorphine (BUP) and samidorphan (SAM). BUP is partial μ opioid partial-agonist and has also been shown to block the action of κ opioid agonists. SAM is a potent, long half-life, sublingually-bioavailable μ opioid antagonist. SAM was included in the combination to block the μ agonist effects of BUP. Fixed ratios of BUP and SAM were co-formulated in a single sublingual tablet (ALKS 5461). Pupillometry and subjective pharmacodynamic effects of varying ratios of BUP:SAM were evaluated in non-addicted opioid experienced subjects. Maximal blockade of pupillary and μ opioid-related subjective and physiologic effects was observed with a 1:1 ratio of BUP:SAM. The 1:1 ratio was therefore carried forward into subsequent clinical evaluation in subjects with MDD and an inadequate response to standard antidepressants. Sequential parallel comparison design (SPCD) was utilized in phase 2 and 3 studies of ALKS-5461. SPCD was employed to minimize placebo effect, which is a major issue in contemporary studies of MDD. ALKS-5461 demonstrated evidence of consistent efficacy vs. placebo in phase 2 and 3 studies. ALKS 5461 was generally well tolerated. The most common AEs included nausea, headache and dizziness. Importantly, there were no AE's suggestive of abuse nor evidence of withdrawal following discontinuation of therapy. Balanced agonist-antagonist opioid modulation with ALKS 5461 is a promising approach for use as adjunctive therapy in patients with MDD who have inadequate response to standard antidepressants. The agonist-antagonist combination may serve to decrease or dampen tone in regions of excess endogenous μ and κ activity and support endogenous tone in regions where it is impaired.

**of special interest to clinicians*

Evaluation of the efficacy of the combination is warranted in other neuropsychiatric disorders where endogenous opioid dysregulation is also implicated.

Learning Objectives:

- Understand the evidence for a role of endogenous opioid dysregulation in major depressive disorder.
- Assess the therapeutic potential of opioid modulation in the treatment of depression resistant to standard antidepressants.

Literature References:

- Ehrlich E, Turncliff R, Du Y, et al: Evaluation of opioid modulation in major depressive disorder. *Neuropsychopharmacology* 2015; 40:1448–1455
- Fava M, Memisoglu A, Thase M, et al: Opioid Modulation With Buprenorphine/Samidorphan as Adjunctive Treatment for Inadequate Response to Antidepressants: A Randomized Double-Blind Placebo-Controlled Trial. *Am J Psychiatry* 2016; 173:499–508

A CLINICAL DEVELOPMENT PROGRAM IN PSYCHIATRY FOR A SELECTIVE KAPPA ANTAGONIST*

Ronald Marcus, Cerecor

Individual Abstract: CERC-501 is a potent and selective oral kappa opioid receptor (“KOR”) antagonist being developed as an adjunctive treatment of major depressive disorder (“MDD”) and to treat substance use disorders. Preclinically, KORs have been shown to play an important role in stress, mood and addiction. CERC-501 has been observed to have positive activity in animal models of depression, nicotine withdrawal and alcohol dependence, and it has been generally well tolerated in three human clinical trials. A PET imaging study demonstrated almost complete saturation of KORs at doses of 10 mg or more at 2.5 h post-dose and substantial and sustained target engagement at least 24 h post-dose. The initial CERC-501 program consists of a proof of concept (POC) trial in nicotine withdrawal (recently completed and results pending) followed by initiation of a Phase 2/3 study in adjunctive MDD in the second half of 2017. The design of the adjunctive depression study will be discussed including methods to minimize patient bias as well as potential biomarkers for the trial. In addition, the results of randomized, double-blind, placebo-controlled, crossover study of subjects who were heavy cigarette smokers and currently not seeking treatment for tobacco use disorder will be presented. The primary objective of this study was to evaluate the effect of CERC-501 15 mg compared to placebo on symptoms of nicotine withdrawal and smoking behaviors, as measured by time to start smoking and number of cigarettes smoked in a 60-minute period, following an 18-hour abstinence.

Learning Objectives:

- To understand the potential clinical indications and development program for KOR antagonist.
- To learn the mechanics of a laboratory nicotine withdrawal study and the results of CERC-501 in that model.

Literature References:

- Naganawa M, Dickinson G, et al. Receptor Occupancy of the k-Opioid Antagonist LY2456302 Measured with Positron Emission Tomography and the Novel Radiotracer 11C-LY2795050. *J Pharm and Experimental Therapeutics* 356:260–266, 2016.

- Rorick-Kehn LM, Witkin JM, et al. LY2456302 is a novel, potent, orally-bioavailable small molecule kappa-selective antagonist with activity in animal models predictive of efficacy in mood and addictive disorders. *Neuro-pharmacology* 77:131–144, 2014.

TRAMADOL AND OTHER OPIOID AGENTS IN REFRACTORY OCD*

Paul Keck, Lindner Center of HOPE/University of Cincinnati

Individual Abstract: Obsessive compulsive disorder (OCD) is a highly burdensome and disabling condition which has shown relatively modest responsiveness to standard therapies, such as pharmacotherapy with selective serotonin reuptake inhibitors and behavioral therapy. Because of that, a number of augmentation strategies have been tried and subsequently studied in OCD, with variable degrees of success. Among those strategies, the use of tramadol and other opioid agents has emerged as a promising approach, partly because of data supporting the hypothesis that the endogenous opioid system may play a role in the pathophysiology of OCD. Not only the rate of OCD in the opioid-dependent populations has been found to be four times higher than the general population, but there have been reports of worsening of OCD during methadone tapering, supporting the hypothesis of a link between the opioid system and OCD. Preclinically, opioid agents have shown to affect stereotypic behaviors in animals and, in humans, open-label trials with tramadol and morphine have suggested a rapid and significant improved in OCD symptoms. A small, placebo-controlled trial of once-weekly oral morphine in patients with OCD who had failed 2 to 6 SSRI trials has shown greater efficacy for morphine compared to placebo, whereas lorazepam did not separate from placebo. Future studies need to further explore the possible therapeutic role of these opioid compounds in OCD.

Learning Objectives:

- To become familiar with the evidence for a dysregulation of the opioid system in OCD.
- To learn about the clinical use of opioid agents in refractory OCD.

Literature References:

- Koran LM, Aboujaoude E, Bullock KD, Franz B, Gamel N, Elliot M. "Double-blind treatment with oral morphine in treatment-resistant obsessive-compulsive disorder". *JClinPsychiatry* 2005 Mar;66(3):353-9.
- Shapira NA, Keck PE Jr., Goldsmith TD, McConville BJ, Elis M, McElroy SL. "Open-label pilot study of tramadol hydrochloride in treatment-refractory obsessive-compulsive disorder". *Depress Anxiety*, 1997; 6(4): 170-3

INFLAMMATION AND OBESITY IN DEPRESSION: NEUROBIOLOGICAL MECHANISMS AND THERAPEUTIC IMPLICATIONS*

Jennifer Felger, Emory University School of Medicine

Overall Abstract: Increased inflammation is observed in a significant proportion of patients with depression and is thought to contribute to disease pathophysiology and symptom severity. Moreover, a major source of inflammation in patients with depression is obesity. Elevations in peripheral markers of inflammation, obesity and metabolic dysregulation have been shown to predict poor antidepressant treatment response. Therefore, understanding the peripheral and neurobiological mechanisms by which inflammation and obesity contribute to depression is important to improve the identification and targeting of therapeutic strategies to

this sub-population of patients with depression. The speakers in this panel will present data from a number of clinical studies demonstrating that patients with increased inflammation and/or obesity may preferentially respond to therapies that reduce inflammation or reverse downstream effects on neurotransmitter systems. Dr. Richard Shelton (UAB) will present recent data indicating that obesity and its associated inflammation is a moderator of the response to standard monoamine antidepressants, and review possible alternative therapies such as treatment with L-methylfolate. Dr. Jennifer Felger (Emory) will present clinical and translational findings indicating that increased inflammation, as well as obesity and markers of metabolic dysregulation, are associated with alterations in dopaminergic corticostriatal circuits in depression, and discuss implications for novel treatment strategies. Dr. Madhukar Trivedi (UT Southwestern) will discuss recent data indicating that inflammatory biomarkers may serve as novel tools for antidepressant medication selection, including findings from the Combining Medications to Enhance Depression Outcomes (CO-MED) trial showing that depressed patients with high plasma interleukin (IL)-17 and/or C-reactive protein (CRP) may preferentially respond to bupropion-plus-escitalopram. Finally, Dr. Mark Rapaport (Emory) will serve as a discussant, synthesizing these findings in the context of the field and in light of data from his group indicating that inflammation and obesity predict antidepressant response to omega-3 polyunsaturated fatty acids. Together, this exciting proposal will integrate novel clinical findings regarding the identification of and treatment implications for patients with increased inflammation and obesity who may not respond to standard antidepressant therapies, while providing evidence of alternative approaches that may have therapeutic benefit in these patients.

Learning Objectives:

- To understand the neurobiological consequences of increased inflammation and obesity in depression, and how these effects may interfere with antidepressant treatment response.
- To identify novel treatment strategies for depressed patients with increased inflammation and/or obesity.

OBESITY AS A MODERATOR OF RESPONSE TO ANTIDEPRESSANTS*

Richard Shelton, University of Alabama at Birmingham

Individual Abstract: Obesity has grown to epidemic proportions in much of the world and is particularly problematic in the U.S. There is strong evidence that prior obesity increases the subsequent risk for depression, suggesting possible causal linkages between the two. This presentation will focus on the obesity as a causal factor for depression and as a possible moderator of antidepressant response. Current evidence supports a path from obesity to the systemic inflammation and metabolic diseases associated with obesity, to depression. However, not only is obesity a possible risk factor for developing depression, it is also a negative moderator of response to monoaminergic antidepressant medications. Increased intra-abdominal fat mass is associated with elevations in pro-inflammatory cytokines such as IL-6 and TNF α , which are known mediators of metabolic diseases such as cardiovascular disease and Type 2 diabetes. There are several hypothesized mechanisms that not only may be related to the genesis or worsening of depression, but also that interfere with the mechanisms of action of antidepressant medications. These mechanisms include: 1) the activation of indoleamine 2,3-dioxygenase, which can deplete tryptophan, the precursor to serotonin and also form kynurenine and its metabolites that can adversely affect dopamine and glutamatergic systems; 2) the activation of nitric oxide synthase, which can deplete tetrahydrobiopterin (BH₄), a cofactor for tryptophan and tyrosine hydroxylases, the rate

limiting steps in the synthesis of serotonin, norepinephrine, and dopamine; and 3) activation of MAP kinase which activates serotonin transporters leading to depletion of synaptic serotonin. Treatments that target obesity and systemic inflammation, or that target the downstream mechanisms that interfere with antidepressant response appear to be useful in treating depression or restoring responsiveness to antidepressants. This presentation will review several possible alternatives including the use of exercise, a reduced glycemic index diet, or l-methylfolate to combat persistent depression in obese patients.

Learning Objectives:

- To better understand the mechanisms by which obesity and systemic inflammation may lead to depression and interfere with the actions of monoaminergic antidepressants.
- To understand possible approaches to managing treatment resistant major depression in face of obesity, including the use of exercise, diet, and l-methylfolate augmentation.

Literature References:

- Shelton R.C., Miller A.H. Eating ourselves to death (and despair): The contribution of adiposity and inflammation to depression. *Progress in Neurobiology* 91:275-299, 2010.
- Shelton R.C., Pencina M.J., Barrentine L.W., Ruiz J.A., Fava M., Zajecka J.M., Papakostas G.I. Association of obesity and inflammatory marker levels on treatment outcome from a double-blind, randomized study of adjunctive l-methylfolate calcium (Deplin) in MDD Patients who are inadequate responders to SSRIs. *J Clin Psychiatry* 76:1635–1641, 2015.

**INFLAMMATION EFFECTS ON REWARD CIRCUITRY AND MOTIVATION:
TREATMENT CONSIDERATIONS FOR DEPRESSION***

Jennifer Felger, Emory University School of Medicine

Individual Abstract: Biomarkers of inflammation such as cytokines and C-reactive protein [CRP] are reliably elevated in a significant proportion of patients with depression, and have been found to predict poor response to standard antidepressant therapies. Furthermore, obesity and visceral adiposity are thought to be a major source of circulating inflammatory cytokines that increase acute phase proteins such as CRP in depression. Both increased plasma CRP and high body mass index in patients with depression have been associated with alterations in corticostriatal reward and motor circuits. With regard to neurobiological mechanisms, our work in both humans and laboratory animals supports the idea that inflammatory cytokines decrease synthesis and release of mesolimbic dopamine to drive changes in reward circuitry and contribute to reduced motivation and motor slowing. Herein, we will present recent data regarding relationships among peripheral blood biomarkers of inflammation (both circulating and leukocyte gene expression), obesity and markers of metabolic disequilibrium, decreased dopamine availability, and fundamental alterations in motivation and motor function in depression. Additionally, we will discuss preliminary findings indicating that decreased corticostriatal functional connectivity in dopaminergic reward circuits may serve as a marker of target engagement in the brain for testing novel anti-inflammatory or pro-dopaminergic treatment strategies to improve motivation and motor deficits in patients with increased inflammation and/or obesity. Together this work supports development of novel therapeutic strategies that can be targeted to this sub-population of depressed patients with high inflammation and obesity, thus personalizing care.

Learning Objectives:

- To understand the neurobiological mechanisms by which inflammation and obesity may affect dopaminergic corticostriatal circuits to lead to motivational and motor deficits in depression.
- To appreciate novel approaches to testing possible therapeutic strategies to treat motivational and motor deficits in depressed patients with increased inflammation and obesity.

Literature References:

- Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, Miller AH. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Mol Psychiatry*, 2016, 21:1358-65
- Mehta D, Raison CL, Woolwine BJ, Haroon E, Binder EB, Miller AH, Felger JC. Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression. *Brain Behav Immun*, 2013, 31:205-15

INFLAMMATORY BIOMARKERS AS VIABLE MODERATORS FOR TREATMENT SELECTION- RESULTS FROM THE COMED TRIAL*

Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: Background: Currently, there are no valid clinical or biological markers to inform treatment selection for depressed patients. Recent evidence suggests that inflammatory biomarkers may personalize selection amongst antidepressant medications with different mechanisms of action.

Methods: Participants of Combining Medications to Enhance Depression Outcomes (COMED) trial who provided plasma samples and were treated with either escitalopram-plus-placebo (n=51), bupropion-plus-escitalopram (n=55), or venlafaxine-plus-mirtazapine (n=60) were included as subjects. Levels of inflammatory biomarkers (Interleukin 17 or IL-17, C-reactive protein or CRP, serum amyloid P component, and alpha-2-macroglobulin) were measured using multiplex immunoassay. Changes in depressive symptom (Quick Inventory of Depressive Symptomatology Self-Report) and side-effect burden (Frequency, Intensity, and Burden of Side-Effects Rating Scale) were assessed with mixed model analyses.

Results: Overall treatment outcomes did not differ among treatment arms. The treatment-arm-by-baseline biomarker level interaction was significant for depression severity with IL-17 (p=0.04) and CRP (p=0.04) and only with CRP for side-effects (p=0.005). Interactions for serum amyloid component P and alpha-2-macroglobulin were insignificant. When treated with bupropion-plus-escitalopram but not with escitalopram-plus-placebo or venlafaxine-plus-mirtazapine, one standard deviation higher IL-17 level at baseline led to 1.6 points greater reduction in QIDS-SR over 3 months. Similarly, higher baseline CRP levels resulted in smaller reductions in QIDS-SR scores with escitalopram-plus-placebo and venlafaxine-plus-mirtazapine but higher reductions with bupropion-plus-escitalopram. Higher CRP levels were associated with higher side-effects only with venlafaxine-plus-mirtazapine. Additional results from the Treatment with Exercise Augmentation for Depression (TrEAD) trial and the role of TNF-Alpha will also be presented.

Conclusions: Inflammatory Biomarkers could serve as a tool for treatment selection in patients with depression.

Learning Objectives:

- Understand the role of inflammatory biomarkers on depressive symptom changes and side effects during antidepressant treatment.
- Using IL-17 and CRP to select specific treatments for depression.

Literature References:

- Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, Warden D, Morris DW, Luther JF, Husain MM, Cook IA, Shelton RC, Lesser IM, Kornstein SG, Wisniewski SR: Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry* 2011; 168:689–701
- Jha MK, Minhajuddin A, Gadad B, Greer TL, Mayes TL, Trivedi MH: Higher baseline plasma levels of interleukin 17 predict better outcomes with bupropion: Novel biomarker for antidepressant medication selection. *Molecular Psychiatry*, submitted.

PHARMACOTHERAPY AND PSYCHOSOCIAL TREATMENT IN FIRST EPISODE PSYCHOSIS STUDIES: MODELS AND OUTCOMES*

Nina Schooler, SUNY Downstate Medical Center

Overall Abstract: In keeping with the theme of ASCP 2017 regarding diverse populations, patients with first-episode psychosis (FEP) represent an important patient group with unique treatment opportunities. There has been increasing research attention to these patients in recent years. The implication in the international community is that groups in Australia and Europe have led this attention, but some United States investigator groups have pursued study of treatments for this population for decades. This panel includes three of these groups and focuses. The panel will focus specifically on the relationship of treatment with anti-psychotics and defined psychosocial treatments for patients with FEP. Three distinct treatment models will be considered. The first is a psychopharmacologic treatment as a platform against which a well-defined psychosocial treatment is compared to a control condition. The second model involves randomization to psychosocial treatments as well as antipsychotic treatments in a 2 by 2 design. The final model compares a treatment approach that integrates pharmacotherapy into a comprehensive treatment program with well-defined psychosocial treatments and compares that to usual care. Examples of pharmacologic treatment as a platform include the Cognitive Enhancement Therapy (CET) studies carried out by Eack and Keshavan. A further example is the supported employment study carried out by Nuechterlein and colleagues. A study comparing long-acting injectable risperidone to oral risperidone and cognitive remediation to a control psychosocial treatment conducted by Nuechterlein and Subotnik provides an example of a fully crossed psychopharmacologic by psychosocial treatment design. The NAVIGATE program compared to Community Care in the RAISE-ETP study carried out by Kane, Robinson and colleagues represent the approach in which pharmacologic treatment is embedded in an integrated intervention. Panelists representing these three groups will describe the approach to pharmacotherapy, how it was implemented and outcomes related to pharmacologic treatments. Dawn Velligan will serve as the panel discussant.

Learning Objectives:

- Understand the relationship of antipsychotic medication administration to the provision of psychosocial treatments in first episode psychosis.

- Be familiar with models for delivery of antipsychotic treatment in first-episode psychosis.

IMPACT OF ANTIPSYCHOTIC MEDICATION DOSE AND ADHERENCE ON IMPROVEMENT DURING COGNITIVE REMEDIATION IN EARLY COURSE SCHIZOPHRENIA*

Shaun Eack, University of Pittsburgh

Individual Abstract: Background: Cognitive remediation interventions are promising for the treatment of cognitive impairments in schizophrenia, yet little is known about the impact of antipsychotic medications on response to such treatments. The purpose of this investigation was to examine the role of antipsychotic dose and adherence on cognitive improvement over the course of two trials of cognitive remediation for patients in the early course of schizophrenia.

Methods: Fifty-eight early course schizophrenia outpatients were randomized to 2-years of either Cognitive Enhancement Therapy (CET; n = 31) or an Enriched Supportive Therapy (EST; n = 27) comparison treatment in Study 1. Study 2 consisted of data from an ongoing multisite trial of CET in 86 early course schizophrenia outpatients randomized to either 18-months of CET (n = 51) or EST (n = 35). All participants completed a comprehensive battery of cognitive assessments prior to and after completing treatment, along with clinician-rated measures, chlorpromazine equivalent dose, and antipsychotic adherence (adherent vs. non-adherent). Linear mixed-effects intent-to-treat models were used to examine the impact of antipsychotic dose and adherence on outcome in CET compared to EST.

Results: Study 1 demonstrated that pre-treatment adherence to antipsychotic medication significantly moderated the differential impact of CET on neurocognitive improvement, $F(2,74) = 3.13, p = .049$. Examination of the moderation effect revealed that participants treated with CET who were more adherent to antipsychotic treatment experienced greater neurocognitive improvement than those who were less adherent to antipsychotics. In Study 2, pre-treatment antipsychotic adherence again moderated the differential benefit of CET on cognitive outcome compared to EST ($F(2,61) = 2.45, p = .094$), particularly by 18 months ($t(61) = 2.21, p = .030$). However, the pattern of findings was different, and indicated a sharp cognitive decline in EST participants who were less adherent to antipsychotic medication. Antipsychotic dose at pre-treatment or follow-up did not significantly predict neurocognitive change in either study (all $p > .344$).

Conclusions: Antipsychotic adherence is an important predictor of neurocognitive response to cognitive remediation in early course schizophrenia. Efforts to enhance medication acceptability and adherence are essential to helping patients benefit from both cognitive and supportive psychosocial interventions.

Learning Objectives:

- Describe the nature of antipsychotic dose and adherence on improvement during cognitive remediation in early course schizophrenia.
- Provide clinical implications to enhance medication acceptability and adherence before participation in cognitive remediation in early course schizophrenia.

Literature References:

- Eack, S. M., Greenwald, D. P., Hogarty, S. S., Cooley, S. J., DiBarry, A. L., Montrose, D. M., & Keshavan, M. S. (2009). Cognitive enhancement therapy for

early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatric Services*, 60(11), 1468-1476.

- Robinson, D. G., Schooler, N. R., John, M., Correll, C. U., Marcy, P., Addington, J., ... & Robinson, J. (2014). Prescription practices in the treatment of first-episode schizophrenia spectrum disorders: data from the national RAISE-ETP study. *American Journal of Psychiatry*.

ANTIPSYCHOTIC MEDICATION EFFECTS IN THE CONTEXT OF PSYCHOSOCIAL TREATMENTS AFTER AN INITIAL EPISODE OF SCHIZOPHRENIA*

Keith Nuechterlein, Semel Institute for Neuroscience & Human Behavior at UCLA

Individual Abstract: The role of antipsychotic medication effects within studies evaluating specific psychosocial treatments after a first episode of schizophrenia is often underappreciated. At UCLA, we conducted two randomized controlled trials in which the role of antipsychotic medication adherence was systematically assessed in the context of particular psychosocial treatments. In a first 18-month study, 69 patients were randomly assigned to supported education/employment or typical vocational rehabilitation after patients were stabilized on oral risperidone. While the primary outcome focus was on the marked increase in competitive employment or schooling with supported education/employment, evaluation of the impact of periods of antipsychotic nonadherence demonstrated that even periods of only moderate nonadherence led to large increases in risk for psychotic exacerbation or relapse. A second study of first-episode schizophrenia patients therefore used randomization to long-acting vs. oral risperidone medication in an attempt to reduce antipsychotic nonadherence. Within the same study, the patients were randomized to cognitive remediation vs. healthy behavior training to determine whether cognitive remediation could improve their cognition and work/school outcomes. Thus, a 2 X 2 design was employed. Results demonstrated that long-acting injectable antipsychotic medication could greatly increase medication adherence and reduce psychotic exacerbation/relapse rates from 33% to 5% for the 12-month clinical trial period. In addition, gains in cognition and work/school functioning were greater with long-acting antipsychotic medication. Covarying for medication adherence when examining the impact of cognitive remediation was found to increase the sensitivity to detecting cognitive gains attributable to cognitive training, as otherwise medication adherence would have contributed to within-group error variance. Through use of a 2 X 2 design, we were able to show that antipsychotic medication adherence and cognitive remediation each made significant contributions to improvements in cognition and work/school functioning after an initial psychotic episode. Taken together, these studies indicate that medication nonadherence plays a very large role in outcome in treatment studies with first-episode schizophrenia patients. Controlling for medication adherence effects through use of long-acting antipsychotic medication has great promise for minimizing relapse and maximizing cognitive and functional recovery after a first psychotic episode. Furthermore, accounting for variability in medication adherence can aid detection of the contributions of specific psychosocial interventions during the early course of schizophrenia.

Learning Objectives:

- To demonstrate the substantial role of medication adherence in outcomes in treatment studies of first-episode schizophrenia patients.

- To illustrate how controlling for medication adherence effects can aid sensitivity to detection of significant effects of specific psychosocial interventions during the early course of illness.

Literature References:

- Subotnik KL, Nuechterlein KH, Ventura J, Gitlin MJ, Marder S, Mintz J, Helleman GS, Thornton LA, Singh IR. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry.* 2011;168:286-292.
- Subotnik KL, Casaus LR, Ventura J, Luo JS, Helleman GS, Gretchen-Doorly D, Marder S, Nuechterlein KH. Long-Acting Injectable Risperidone for Relapse Prevention and Control of Breakthrough Symptoms After a Recent First Episode of Schizophrenia. A Randomized Clinical Trial. *JAMA Psychiatry.* 2015;72:822-829.

PSYCHOPHARMACOLOGICAL TREATMENT IN THE RAISE-ETP STUDY: A MANUAL AND COMPUTER DECISION SUPPORT SYSTEM BASED INTERVENTION WITHIN A COMPREHENSIVE FIRST EPISODE SPECIALTY CARE PROGRAM*

Delbert Robinson, Hofstra NS-LIJ School of Medicine

Individual Abstract: Objective: RAISE-ETP compared with a cluster randomized design NAVIGATE, a comprehensive treatment program for first-episode psychosis, to clinician-choice treatment over a two year treatment period. NAVIGATE treatment included medication treatment, individual therapy to promote resiliency, psychoeducation about psychosis and its treatment and supports for work and school participation provided within an integrated team model. Quality of life and both psychosis and depressive symptom outcomes were better for NAVIGATE participants. Compared with prior comprehensive first-episode psychosis interventions, NAVIGATE medication prescription included unique elements of 1) detailed specific first-episode psychotropic medication guidelines and 2) a computerized decision support system to facilitate shared decision making regarding prescriptions. We will present comparisons of the psychotropic medications prescribed and the side effects participants experienced.

Methods: Prescription data were obtained using the Service Use and Resource Form administered monthly. At baseline, 3, 6, 12, 18 and 24 months, participants reported whether they were experiencing any of 21 common antipsychotic side effects. Concurrently, vital signs were obtained and fasting blood samples collected.

Results: Over the 2 years, the 223 NAVIGATE participants compared to the 181 clinician-choice participants had more medication visits, were more likely to be prescribed an antipsychotic and also an antipsychotic conforming to NAVIGATE prescribing principles and were less likely to be prescribed an antidepressant. NAVIGATE participants experienced fewer side effects and also gained less weight; other vital signs and cardiometabolic laboratory findings did not differ between treatment conditions.

Conclusions: As part of comprehensive care services, medication prescription can be optimized for first-episode psychosis, contributing to better symptom outcomes with less side effect burden than standard care.

Learning Objectives:

- At the completion of the presentation, listeners will be able to discuss medication outcome differences between comprehensive treatment programs and usual care.
- At the completion of the presentation, listeners will be familiar with issues related to implementing medication decision support systems in community treatment facilities.

Literature References:

- Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. *Am J Psychiatry*. 2016 Apr 1;173(4):362–72.
- Robinson DG, Schooler NR, John M, Correll CU, Marcy P, Addington J, et al. Prescription practices in the treatment of first-episode schizophrenia spectrum disorders: data from the national RAISE-ETP study. *Am J Psychiatry*. 2015 Mar 1;172(3):237–48.

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

Tuesday Mid-Morning Panel Sessions

TARGETING TREATMENT NEEDS IN WOMEN'S MENTAL HEALTH*

Marlene Freeman, Massachusetts General Hospital

Overall Abstract: As we recognize the specific needs within a diverse population, areas of women's mental health warrant novel treatment approaches and clinical research. Psychiatric disorders among mothers are important to detect and treat, not only because of the great toll that they take on the individual women, but also because children are impacted substantially by the burden of maternal psychiatric illness. Dr. Holly Swartz will address targeted psychotherapies for mothers and the impact upon mothers and their children. Mothers were randomly assigned to treatment with brief interpersonal psychotherapy or supportive psychotherapy. Dyads were assessed every three months for one year. Symptoms and functioning of mothers and children improved significantly over time with no between-group differences. Improvement in mothers' depressive symptoms was associated with improvement in child functioning in a time-lagged fashion, with children improving 3 -6 months after mothers improved. Data also reveal challenges for the treatment of women with histories of neglect. Postpartum depression (PPD) is specifically associated with maternal morbidity, as well as negative consequences on maternal-infant bonding and childhood outcomes. Dr. Samantha Meltzer Brody will present new data on a novel neurosteroid treatment for refractory PPD. SAGE-547, a proprietary formulation of allopregnanolone, was evaluated for the treatment of severe PPD in a randomized, placebo-controlled Phase 2 trial. In this study, investigators enrolled 21 patients within 6 months postpartum, with severe PPD (HAM-D >26). SAGE-547 or placebo was administered inpatient by IV for 60 hrs. The primary endpoint was reduction of HAM-D scores vs placebo at 60 hrs. Patients were followed for 30 days to assess maintenance of effect and safety. SAGE-547 patients experienced a mean HAM-D reduction of >20 points at 60 h, 12 points greater than placebo (p=0.008). These improvements began at 24 h and were maintained through the 30-day follow up. Remission from depression (HAM-D ≤7) was achieved for 70% of the SAGE-547 group versus 9% of the placebo group at 60 h (p=0.008), which was maintained through 30 d (p=0.03). SAGE-547 was generally well tolerated. Infertility and the course of psychiatric disorders is an area that has received little formal study. It is appreciated that infertility treatment is often associated with high levels of perceived stress, although the course of mood disorders during infertility treatment has not been well studied. Dr. Freeman will

**of special interest to clinicians*

present data on depressive relapse rates among women with previous diagnoses of mood disorders during the course of infertility treatment, as well as risk factors, and biomarkers. The aims of this naturalistic prospective study were to delineate the predictors of depressive relapse in women with histories of depressive episodes (diagnoses of MDD and bipolar disorder) during infertility treatment. Patients were each followed for six months, during which they were tracked with respect to: course of mood symptoms, psychotropic medication use, psychotherapy, perceived stress, partner support, and all infertility based treatments and interventions. A subsample participated in the collection of biomarkers. Depressive relapse rates were high and were not significantly different between psychotropic medicine maintainers and discontinuers. Higher scores on the Perceived Stress Scale and C-reactive protein levels were associated with depressive relapse.

Learning Objectives:

- To understand the different contexts by which depression in women may present across specialized situations across the reproductive lifespan.
- To approach targeted treatment development that takes into account needs of patients in specific psychosocial and biologic environments.

BRIEF PSYCHOTHERAPY FOR MATERNAL DEPRESSION: IMPACT ON SCHOOL AGE CHILDREN*

Holly Swartz, University of Pittsburgh School of Medicine

Individual Abstract: Objectives: Treatment of maternal depression with psychotherapy has been shown to confer indirect benefit to school-age offspring with psychiatric disorders. The current study sought to understand mechanisms by which improvement in depressed mothers treated with brief psychotherapy produces changes in children with internalizing disorders. Methods: Participants were mothers with major depressive disorder and their children, age 7-18, with at least one internalizing disorder. Mothers were randomly assigned to nine sessions of either brief interpersonal psychotherapy (IPT-MOMS; n=85) or brief supportive psychotherapy (BSP; n=83). Children were treated openly in the community. Independent assessors evaluated dyads every three months over one year.

Results: Symptoms and functioning of mothers and children improved significantly over time with no between-group differences. Improvement in mothers' depressive symptoms was associated with improvement in child functioning in a time-lagged fashion, with children improving 3 -6 months after mothers improved. Analyses showed a significant association between improvement in maternal depression and child functioning after a three month lag ($\beta = 0.14, p = 0.03$), an association that proved even stronger with a 6 month lag ($\beta = 0.2, p = 0.01$). In a subset of dyads where children had internalizing disorders only (n=63), child-reported increase in positive parenting strategies (acceptance) by mothers mediated 6-month lagged associations between maternal and child outcomes but reductions in negative parenting strategies (psychological control) did not. Change in acceptance from 0 to 6 months predicted improvement in child depression from 0 to 9 months ($\beta = -0.27, p = 0.01$). Maternal history of childhood trauma moderated the mediational model such that improved positive parenting no longer explained lagged improvement in child outcome when mothers had histories of childhood emotional neglect.

Conclusions: In dyads comprised of depressed mothers and school age children with internalizing disorders, increased use of positive parenting strategies among mothers

explained the lagged relationship between improvement in maternal symptoms and improvement in child functioning. This pattern was not observed among mothers with histories of early emotional neglect. Interventions that directly enhance positive parenting and more rapidly change these behaviors may hasten improvement in offspring. Mothers with histories of emotional neglect may need additional services to help them develop positive parenting strategies.

Learning Objectives:

- Recognize the importance of positive parenting strategies on child outcomes.
- Identify the negative impact of early emotional neglect on mothers and their offspring.

Literature References:

- Swartz HA, Cyranowski JM, Cheng Y, Zuckoff A, Brent DA, Markowitz JC, Martin S, Amole MC, Ritchey F, Frank E. Brief psychotherapy for maternal depression: Impact on mothers and children. *J Am Acad Child Adol Psychiatry* 2016; 55 (6):495-503
- Zalewski M, Cyranowski JM, Cheng Y, Swartz HA. Role of maternal childhood trauma on parenting among depressed mothers of psychiatrically ill children. *Depress Anxiety*; 2013; 30 (9): 792-799.

RESULTS FROM A PHASE 2 TRIAL OF SAGE-547 IN SEVERE POSTPARTUM DEPRESSION*

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

Individual Abstract: Objective/Background: Antidepressants are commonly used to treat PPD, but there are no pharmacological therapies specifically approved for PPD. Following childbirth, the levels of allopregnanolone, a neuroactive steroid drop precipitously¹; preclinical evidence suggests that this drop contributes to PPD onset². SAGE-547 injection, a proprietary formulation of allopregnanolone, was evaluated for the treatment of severe PPD in a randomized, placebo-controlled Phase 2 trial.

Methods: The study enrolled 21 patients <6 months postpartum, with severe PPD (HAM-D >26). Patients were randomized 1:1 to either SAGE-547 injection or placebo by IV for 60 h. The primary endpoint was reduction of HAM-D scores versus placebo at the 60 h time point. Patients were followed through 30 days to assess maintenance of effect and safety parameters. Secondary efficacy endpoints included assessment using the Montgomery–Åsberg Depression Rating Scale (MADRS).

Results: SAGE-547 patients showed a mean HAM-D reduction of greater than 20 points at 60 h. This reduction was 12 points greater than placebo (p=0.008). These improvements began at 24 h and were maintained through the 30 day follow up. Remission from depression (HAM-D ≤7) was achieved for 70% of the SAGE-547 group versus 9% of the placebo group at 60 h (p=0.008), which was maintained through 30 d (p=0.03). SAGE-547 was generally well tolerated, with no serious adverse events, deaths, or discontinuations.

Conclusion/Discussion: SAGE-547 treated patients demonstrated rapid and sustained reductions in the HAM-D score versus placebo. These data replicate prior open-label data for SAGE-547 in PPD and support ongoing development of this compound and mechanism in PPD.

Learning Objectives:

- Discuss the proposed mechanism of action of Sage-547.

- Examine the robust treatment response in this double-blind study with short time of response.

Literature References:

- MAGUIRE, J. & MODY, I. 2008. GABAAR Plasticity during Pregnancy: Relevance to Postpartum Depression. *Neuron*, 59, 207-213.
- SCHILLER, C. E., SCHMIDT, P. J. & RUBINOW, D. R. 2014b. Allopregnanolone as a mediator of affective switching in reproductive mood disorders. *Psychopharmacology (Berlin)*, 5, 3557-3567.

RISK OF DEPRESSIVE RELAPSE IN WOMEN UNDERGOING TREATMENT FOR INFERTILITY*

Marlene Freeman, Massachusetts General Hospital

Individual Abstract: Objective: Mood disorders are prevalent in women of reproductive age, and their course across infertility treatment and implications for clinical management have received little systematic study. The aims of the study were to delineate the predictors of depressive relapse in women with histories of depressive episodes (diagnoses of major depressive disorder (MDD) and bipolar disorder) during infertility treatment and assess potential biomarkers of risk.

Methods: This was a prospective naturalistic investigation to assess the course of MDD and bipolar depression across treatment for infertility. Participants included women planning undergoing assisted reproductive technology (ART). Patients were each prospectively followed for six months, during which they were tracked with respect to: course of mood symptoms, antidepressant, mood stabilizer, and other medication use, psychotherapy, perceived stress, partner support, use of gonadotropins or other hormonal interventions, and all infertility based treatments and interventions. A subsample participated in the collection of biomarkers.

Results: Of the women in the study with a diagnosis of MDD (N=25), the overall relapse rate was 44%. The rate of relapse did not significantly differ between maintainers of antidepressants (N=15; 40.0%) and medication discontinuers (N=10; 50.0%). Among women with diagnoses of bipolar disorder (N=13), the relapse rate was 4/13 (30.8%); none of the medication discontinuers relapsed (N=3), and 40.0% of the maintainers relapsed. Scores on the Perceived Stress Scale (PSS) were correlated with relapse risk (OR=1.17 [95% CI: 1.08 – 1.26], p=0.0002). C-reactive protein (CRP) levels were associated with depressive relapse (OR=1.92 [95%CI: 1.43-2.55], p<0.0001), although blood cortisol and IL-6 levels were not.

Conclusions: The risk of relapse among women with mood disorders undergoing infertility treatment is high. Stress and inflammation may contribute to relapse risk. Maintenance psychotropic medication continuation does not necessarily confer adequate protection against relapse to depressive episodes in this context. There is a great need for additional clinical strategies for women with histories of depressive episodes undergoing ART.

Learning Objectives:

- To assess rates of depressive relapse in women with histories of mood disorders undergoing infertility treatment.
- To assess risk factors for depressive relapse in women undergoing infertility treatment.

Literature References:

- Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA* 2006;295:499-507.
- Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007;22:1506-12.

THE DEVELOPMENT AND SELECTED PERFORMANCE OF PATIENT REPORTED OUTCOMES (PRO) IN PSYCHOPHARMACOTHERAPY TRIALS – IS THE JUICE WORTH THE SQUEEZE? A REVIEW OF INITIATIVES BY THE FDA, NIH, AND THE ALCOHOL CLINICAL TRIALS INITIATIVE (ACTIVE)

Stephanie O'Malley, Yale University School of Medicine

Overall Abstract: The Alcohol Clinical Trials Initiative (ACTIVE) was formed as a public-private partnership including members of Academia, Industry, and Government (NIAAA, NIDA, and FDA) to better understand and define best methods/practices in alcohol clinical trials. One issue currently under consideration is the selection of an appropriate patient rated measure of alcohol related consequences to assess the benefits of pharmacological treatment. This choice is informed by the FDA's guidance to Industry about Patient Rated Outcomes. Prior alcohol related consequences measures were found to be lacking, and a new measure, the IMBIBE, was developed initially by industry and is now being further evaluated by ACTIVE. With funding from the NIH, a set of person-centered measures (PROMIS®) have also been developed to evaluate and monitor physical, mental and social health that could potentially be used in clinical trials.

The focus of this symposium will be on Patient Rated Outcomes of relevance to alcohol and tobacco clinical trials. Dr. O'Malley (Yale School of Medicine) will introduce the symposium and describe the structure of ACTIVE and its mission. Dr. Elektra Papadopoulos (FDA) will provide an overview of the FDA guidance on how to develop patient-reported outcomes and their use in medical product development to support labeling claims. Dr. Daniel Falk (NIAAA) will then review the rationale for the development of a new PRO measure of alcohol related consequences, the IMBIBE, that was intended to address limitations of prior alcohol consequences measures. The psychometric properties of the IMBIBE, and how it performs in two pharmacotherapy trials will be presented. Dr. Maria Edelen (Rand Corporation) will provide an overview of the Patient-Reported Outcomes Measurement Information System (PROMIS) Program which is an NIH-funded effort to develop psychometrically-sound measures. She will specifically review the development of the Tobacco Item Banks, and briefly discuss the Alcohol Consequences Item Bank. Finally, Dr. Bernard Silverman (Alkermes) will summarize the information presented and discuss the potential value of PROs as secondary endpoints in clinical trials to support labeling claims.

Learning Objectives:

- Describe the FDA's current recommendations for developing a Patient Rated Outcome to support labeling claims.
- Identify the strengths and weaknesses of potential patient rated outcomes relevant to alcohol and tobacco-related consequences.

PATIENT-REPORTED OUTCOMES TO CAPTURE THE PATIENT VOICE IN DRUG DEVELOPMENT: A REGULATORY PERSPECTIVE

Elektra Papadopoulou, Food and Drug Administration

Individual Abstract: Clinical benefit is defined as a positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives. Well-defined and reliable assessments form the basis of FDA's conclusions of clinical benefit, which may then be described in labeling as claims that represent the concepts measured. Patient-reported outcome (PRO) instruments capture aspects of how patients feel and function directly from the patients themselves. PRO instruments should measure something meaningful to patients with the disease or condition of interest and they should be valid, reliable, and able to detect change. Evidence of patient or caregiver input is central to evaluating whether an instrument is fit-for-purpose. Planning a PRO measurement strategy to demonstrate a medical product's clinical benefit should be done as early as possible in product development and in collaboration with FDA. FDA has developed guidance describing its review of PRO instruments as well as pathways for communication with stakeholders with the purpose of advancing the development and implementation of PRO instruments to successfully capture the patient voice in drug development.

Learning Objectives:

- Describe the key considerations for FDA review of PRO instruments to support labeling claims.
- Describe the major pathways for engagement with FDA's Center for Drug Evaluation and Research regarding PRO instrument development and validation.

Literature References:

- FDA. Food and Drug Administration guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims. Federal Register 2009.
- FDA. Food and Drug Administration guidance for industry on qualification process for drug development tools. Federal Register 2014.

ALCOHOL CLINICAL TRIALS INITIATIVE (ACTIVE) VALIDATION OF A POTENTIAL PATIENT-REPORTED OUTCOME MEASURE OF ALCOHOL-RELATED CONSEQUENCES (THE IMBIBE) AND ITS USE AS AN ENDPOINT IN ALCOHOL PHARMACOTHERAPY TRIALS

Daniel Falk, NIAAA/NIH

Individual Abstract: A wide variety of efficacy endpoints currently exist in clinical trials for the treatment of alcohol use disorder (AUD). While most primary efficacy endpoints are variations of alcohol consumption (often assessed via a timeline followback methodology), patient-reported endpoints of alcohol-related consequences are regularly evaluated as secondary endpoints. Despite their frequent use and appealing face-validity, the current standard assessment instruments of alcohol-related consequences have not been sufficiently developed for their use as patient-reported outcomes (PROs) in alcohol pharmacotherapy labeling claims. As a remedy, a new measure of alcohol-related consequences, the Impact on Beverage Intake on Behavior (IMBIBE), was developed initially by industry and is now being further evaluated by the Alcohol Clinical Trials Initiative (ACTIVE) for use as a PRO. This symposium will briefly review the commonly used instruments used in the alcohol field and the development of the IMBIBE, followed by new data from ACTIVE on the

psychometric properties of the IMBIBE and its performance as an efficacy endpoint in two clinical trials. Data were from two recent randomized placebo-controlled pharmacotherapy clinical trials that evaluated the efficacy varenicline (Chantix®) as a treatment for AUD. Factor analysis indicated that alcohol-related consequences of the IMBIBE represented a single unitary construct with adequate reliability and validity. Construct validity was enhanced throughout IMBIBE development by panels of experts and patients with alcohol-related problems. Analyses of criterion validity demonstrated a moderate-to-strong correlation of the IMBIBE with levels of alcohol consumption. Despite evidence of desirable psychometric properties, a significant varenicline treatment effect was not observed in one of the two trials when the IMBIBE was used as an endpoint, even though significant treatment effects were found using alcohol consumption endpoints in both trials. Further research is needed to evaluate the psychometrics and performance of the IMBIBE in additional clinical trials to support its use as PRO.

Learning Objectives:

- To gain familiarity of the strengths and limitations of measures of alcohol-related consequences commonly used in the alcohol field.
- To gain an appreciation of the resource-intensive efforts required to develop a potential PRO, the IMBIBE, and to understand its psychometric properties and performance in two recent clinical trials.

Literature References:

- Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, Green AI, Pettinati HM, Ciraulo DA, Sarid-Segal O, Kampman K, Brunette MF, Strain EC, Tiouririne NA, Ransom J, Scott C, Stout R, NCIG (National Institute on Alcohol Abuse and Alcoholism Clinical Investigations Group): A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *J Addict Med* 2013; 7:277-86.
- Werner M, Rentz A, Frank L, Bowman L, Duhig A, Moss H: Participant consequence measures. Presented at the annual meeting of the Research Society on Alcoholism, Washington, DC 2009.

THE PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS) PROGRAM: AN NIH-FUNDED EFFORT TO DEVELOP A PSYCHOMETRICALLY-SOUND PRO ITEM BANK: TOBACCO AND ALCOHOL BANKS

Maria Edelen, RAND Corporation

Individual Abstract: Recognizing the lack of standardized measurement in the assessment of patient-reported outcomes, scientists from academic institutions and the NIH formed a cooperative group in late 2004 to transform health measurement with the Patient Reported Outcomes Measurement Information System (PROMIS®). Adapting the World Health Organization's tripartite framework of physical, mental, and social health, PROMIS investigators have since developed and calibrated multiple item banks covering a wide range of health domains. PROMIS methods draw on modern measurement theory and advanced computerized assessment to permit flexible assessment, increase measurement accuracy, and reduce response burden. PROMIS investigators have subsequently aimed to disseminate high-quality assessments in clinical research and to build validity evidence in health-care delivery settings. This talk will focus on PROMIS item banks assessing constructs associated with alcohol (alcohol use, consequences and expectancies) and smoking (dependence;

coping, emotional and sensory, psychosocial, and health expectancies; and social motivations). The alcohol and smoking banks were developed and refined using item response theory based on data from large national samples. The result is a collection of item banks covering a wide range of content and displaying strong psychometric properties. Researchers wishing to use the PROMIS item banks to assess alcohol or smoking-related constructs can choose from a variety of short forms, tailored assessments or computer adaptive administrations. Evidence for the validity of scores based on assessments from these banks across mode of administration is accumulating, including their associations with other measures of similar constructs as well as outcomes of interest, providing a strong basis for their continued uptake.

Learning Objectives:

- Gain a familiarity with the PROMIS measurement framework.
- Understand what aspects of smoking and alcohol-related PROMIS assessments are available.

Literature References:

- Edelen MO, Stucky BD, Hansen M, Tucker JS, Shadel WG, Cai L. The PROMIS Smoking Initiative: initial validity evidence for six new smoking item banks. *Nicotine Tob Res.* 2014;16(3).
- Pilkonis PA, Yu L, Dodds NE, Johnston KL, Lawrence SM, Daley DC. Validation of the alcohol use item banks from the Patient-Reported Outcomes Measurement Information System (PROMIS). *Drug and alcohol dependence.* 2016;161:316-22.

MODEL-BASED APPROACHES TO ASSIST CLINICAL DEVELOPMENT OF PSYCHIATRIC PRODUCTS

Hao Zhu, U.S. FDA

Overall Abstract: Quantitative clinical pharmacology tools, such as modeling and simulation, can assist clinical development, optimize clinical trial design, and inform appropriate use of a psychiatric product. In this panel, we would like to share some of the FDA's experience on applying these tools in clinical development of various psychiatric products.

The first presentation will focus on a quantitative exposure-response model that is used to describe blood pressure and heart rate changes following the administration of methylphenidate. The model is based on clinical observations for methylphenidate products with different release characteristics. The results indicated that blood pressure and heart rate changes are highly correlated with methylphenidate concentration. Additionally, this model provides a quantitative tool to predict blood pressure and heart rate changes for a novel methylphenidate product that is under development, and allows a clinical investigator or developer to design an effective safety monitoring plan.

The second presentation will provide a summary of dosing regimens of various long acting injectable antipsychotics, which are derived from population pharmacokinetic modeling and simulations. In recent years, several long acting injectable antipsychotics have been marketed in the U.S. These products share a unique feature that all the formulations are designed to release drug over a prolonged time period, which leads to challenges in providing appropriate dosing to patients. Modeling and simulations have been applied to assist the design of dosing regimens in patients. For instance, a population pharmacokinetic simulation was conducted to ensure that the exposure of the active moiety can achieve desirable level rapidly following a

loading dosing of two injections of Invega Sustenna® within a week. In addition, simulations have been used to define injection windows for flexibility that can be provided for patients who cannot follow scheduled visits without compromising the treatment effect. Furthermore, different reinitiation dosing regimens have been designed on the basis of simulations for multiple products in patients missing an injection over various time intervals (e.g., weeks or months after the scheduled visits), so that the effective exposure may be re-achieved over the shortest possible time. These modeling and simulation findings have been used to support labeling for recently approved long acting injectable antipsychotics. The third presentation will discuss the treatment duration in pivotal clinical efficacy and safety trials used to support product approval of antipsychotics in the U.S. Currently, most clinical trials require at least 6-8 weeks of double-blind phase to assess the treatment effect. By checking the clinical observations from different antipsychotics submitted to the FDA, the time courses of symptom improvement between the treatment group and placebo group have been assessed. It has been shown that the treatment effect at shorter treatment duration provides consistent results and conclusions as compared to that observed at week 6 or 8. Hence, it is suggested that short treatment duration may be an alternative for future pivotal clinical efficacy and safety trials for antipsychotics. Overall, this panel intends to share with audience that quantitative clinical pharmacology tools can be used to facilitate clinical trial design and has been used to inform proper use of psychiatric products in patients.

Learning Objectives:

- To understand the utility of quantitative clinical pharmacology tools in the drug development for psychiatric products.
- To understand the quantitative clinical pharmacology basis for regulatory recommendations on proper use of certain psychiatric products.

EXPOSURE-RESPONSE ANALYSIS OF BLOOD PRESSURE AND HEART RATE CHANGES FOR METHYLPHENIDATE IN HEALTHY ADULTS

Yaning Wang, Center for Drug Evaluation and Research, US Food and Drug Administration

Individual Abstract: Purpose: To evaluate the exposure-response (E-R) relationships of blood pressure (BP) and heart rate (HR) changes in healthy adults taking methylphenidate (MPH).

Methods: Intensive time profiles of BP and HR from healthy adults in placebo and MPH treatment arms of seven clinical trials from NDAs submitted to the FDA were utilized in this analysis. The final model contains a circadian rhythm model to quantitatively describe the BP or HR change over time (24 hours) in the placebo arms and an exposure-response model to quantify the drug induced changes on BP and HR following the methylphenidate concentration changes. An internal model validation was performed to compare the predicted values and the observed values. A meta-database based on a systemic literature search was constructed and used for external validation of the developed models.

Results: Circadian rhythm models with three sine functions with periods of 24 h, 12 h, and 6 h were developed to quantify the time profiles of BP and HR in placebo arms. Linear models were found to best describe the correlations between MPH concentrations and BP and HR changes. The BP and HR changes were highly dependent on the shapes of MPH pharmacokinetic (PK) profiles without an apparent time delay. MPH has the greatest effect

on HR, followed by systolic blood pressure (SBP), and diastolic blood pressure (DBP). The typical values (relative standard error, RSE) of the slopes of the linear relationships were estimated to be 0.311 mmHg per 1 ng/mL (9.30%) for SBP, 0.186 mmHg per 1 ng/mL (9.80%) for DBP, and 0.668 bpm per 1 ng/mL (5.20%) for HR. Internal validation revealed that the developed models could adequately describe the circadian rhythms of HR and BP in placebo arms and the E-R relationships of MPH. External validation showed the models had good predictive capability of the literature data.

Conclusions: The developed models adequately characterized the circadian rhythm and the MPH-induced effects on BP and HR. The changes in BP and HR following the treatment with MPH are highly correlated with MPH blood levels. The time courses of BP and HR are consistent with the MPH pharmacokinetic profiles. These models could also be used to predict the BP and HR profiles for new MPH formulations whose release characteristics and the pharmacokinetic profiles are unique. More importantly, a clinical investigator or a developer may apply this model to design a safety monitoring plan.

Learning Objectives:

- To understand how model-based approaches can be used to assist clinical development of psychiatric products.
- To understand how exposure-response analysis can be applied to quantify the relationship between drug concentration and relevant adverse events.

Literature References:

- U.S. Food and Drug Administration. Bioequivalence Guidance on Methylphenidate Hydrochloride. <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf>> (2015).
- Kimko, H. et al. Population pharmacodynamic modeling of various extended-release formulations of methylphenidate in children with attention deficit hyperactivity disorder via meta-analysis. *Journal of pharmacokinetics and pharmacodynamics* 39, 161-76 (2012).

POPULATION PHARMACOKINETIC MODELING AND SIMULATION TO DETERMINE DOSING STRATEGIES FOR LONG ACTING INJECTABLE ANTIPSYCHOTICS

Hao Zhu, U.S. Food and Drug Administration

Individual Abstract: Objective: Long acting injectable (LAI) antipsychotics have been developed to prolong dosing intervals, and to reduce dosing frequency with the intention to improve compliance and disease control. The prolonged and sustained drug release from LAIs can be achieved through various mechanisms. Because of the unique release feature of long acting injections, dosing strategy determination may be complicated. Health providers' general experience based on drugs with short half lives may not be useful. Sometimes, testing of alternative dosing regimens, such as reinitiation regimen of long acting injections in clinical trials is impractical and unethical. In this presentation, we plan to share FDA's experience on using modeling and simulation to determine dosing regimens for long acting injections under various scenarios.

Methods: The FDA's recent experience by using population pharmacokinetic modeling and simulation from different long acting antipsychotics will be summarized. Typical modeling and simulation approaches applied to derive dosing strategies will be provided. Resulting

dosing regimens, based on modeling and simulation, for various approved long acting injectable antipsychotics will be shared.

Results: Dosing regimens for multiple long acting injectable antipsychotics have been developed on the basis of population pharmacokinetic modeling and simulations. These products include Invega Sustenna® (Paliperidone Palmitate one month injection), Invega Trinza® (Paliperidone Palmitate three month injection), Abilify Maintenna® (Aripiprazole one month injection), and Arstada® (Aripiprazole lauroxil one month injection). Details on modeling and simulation approach will be discussed. Based on the strong evidence generated from the simulations, relevant dosing instructions have been included in the U.S. package insert of all these products. These instructions include an allowable dosing window that provides flexibility in regular clinical visits for injection. A loading dose regimen that allows effective blood concentration to be achieved in a relatively short time after starting the long acting treatment was designed. In addition, re initiation dosing strategy that brings the blood concentration back to the effective level for patients discontinuing the treatment with various time intervals was also provided. Dosing regimens that ensure safe use of long acting injectable antipsychotics for patients receiving concomitant medications or with compromised renal function were also determined.

Conclusions: Modeling and simulation is a useful tool to design dosing regimens and to facilitate proper use of long acting injectable antipsychotics. This tool fully uses the information obtained from the existing pharmacokinetic trials and derives the dosing instructions for situations difficult to handle in clinical practice and impractical to evaluate in clinical efficacy and safety trials. This approach improves the efficiency in product development and ensures the safe use of long acting injectable antipsychotics. Hence, we expect this approach will be commonly applied in future development program of long acting injectable antipsychotics.

Learning Objectives:

- How to utilize modeling and simulation for developing alternate dosing regimens.

SHORTENING THE DURATION OF ACUTE SCHIZOPHRENIA REGISTRATION TRIALS IS A POSSIBILITY

Islam Younis, US Food and Drug Administration

Individual Abstract: Background: Registration trials for acute schizophrenia indication are placebo controlled and typically of 6 week duration. Shortening the duration of these trials would reduce patient burden and ethical objections to prolonged exposure to placebo. It could also reduce the potential bias due to higher dropout rates in longer trials. The objective of the analysis was to evaluate the feasibility of conducting a 3 or 4-week registration trial for demonstration of efficacy and safety for drugs indicated for acute schizophrenia.

Methods: A master database consisting of efficacy, safety and demographic information from eight new drug applications (NDA) indicated for schizophrenia, approved between 2001 and 2015, was created. The database included longitudinal, subject level information of Positive and Negative Syndrome Scale (PANSS,), demographics and adverse events data. The mean change from baseline in PANSS (primary endpoint) at 3 and 4 weeks was estimated using a mixed model repeated measure (MMRM) analysis adjusted for baseline PANSS for each trial in the database and the trial outcome was compared with the original pre-specified analysis (6-week duration). Concordance and discordance rates with the 6-

week trial results were examined and the implication of a shorter trial on the sample size requirements was assessed. The proportion of major adverse events associated with atypical antipsychotics evident at early endpoints was assessed.

Results: The master database encompassed longitudinal, subject level PANSS and adverse event information from 32 studies, both fixed and flexible dose trials, across 8 NDA's, consisting a total of 14215 subjects (Placebo: 3531, Drug: 10684) and 86 treatment arms including active controls. The global mean change from baseline in PANSS over time demonstrated separation of placebo and drug effect as early as 2 weeks consistently across all drugs, by gender, by region and by type of dosing (fixed vs flexible). The overall concordance and discordance rates for Week 3 and Week 4 endpoints compared with the pre-specified 6 week endpoint were 83% & 17% and 93% & 7%, respectively. A concordance rate of at least 90% was evident for each of the individual drugs at four weeks, except Quetiapine-XR (77%). Adequate occurrence (at least 2%) of major adverse events such as akathisia, somnolence, agitation, tachycardia, extra-pyridamidal symptoms, and dizziness were evident as early as 2 weeks. Considering the placebo corrected mean change from baseline PANSS at week 4, a 32% higher sample size will be required as compared to week 6 endpoint, however the dropout rates at week 4 were 30% lower than at week 6.

Conclusions: The comprehensive analysis based on the largest database of randomized controlled trial of atypical anti-psychotics suggested that the shorter, four-week trial can adequately provide evidence of efficacy and safety similar to a six-week trial and is a feasible option.

Learning Objectives:

- Illustrate that shorter duration of schizophrenia trials is feasible.

DEVELOPMENT OF ANTIDEPRESSANTS WITH NOVEL MECHANISMS OF ACTION*

George Papakostas, Massachusetts General Hospital

Overall Abstract: Mood disorders are among the most common psychiatric conditions. Symptoms can lead to significant disability, which results in impairments in overall quality of life. Though there are many approved treatments for major depressive disorder—including typical and atypical antipsychotics, selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors—only a minority of patients experience full symptomatic remission with these therapies. Therefore, it is imperative for drug discovery to continue towards the development of compounds with novel, preferably non-monoaminergic mechanisms of action. Towards this end, there are several exciting paths of development underway and, clearly, the current pipeline of antidepressant candidate treatments is shifting towards medications with novel mechanisms, which may lead to important, life-changing discoveries for patients with severe disease. In the present panel, we will discuss three such specific efforts.

Learning Objectives:

- At the conclusion of this talk, participants will be better able to describe the development process for three novel, non-monoaminergic molecules for the treatment of mood disorders.
- At the conclusion of this talk, participants will be better able to describe the potential role of neuroinflammation, neurogenesis, and neurosteroids in the treatment of depression.

THE NEUROGENIC ANTIDEPRESSANT COMPOUND, NSI-189, SHOWS POTENTIAL AS A BROAD NEUROTROPHIC AGENT*

Karl Johe, Neuralstem, Inc.

Individual Abstract: The inhibition of adult hippocampal neurogenesis has been implicated in a number of diseases that affect cognition and/or emotion such as major depressive disorder. NSI-189 was selected for its neurogenic activity from a compound screening campaign based on in vitro neurogenesis assay utilizing human hippocampus-derived neural stem cells. NSI-189 is a benzylpiperazine-aminiopyridine (mol.wt. 366), a novel chemical entity that is orally active and rapidly bioavailable in the brain, that stimulates neurogenesis in normal healthy young adult mice in vivo. It also increases their hippocampal volume and demonstrates antidepressant activities in mouse models of depression such as novelty suppressed feeding. In a randomized, placebo-controlled, double-blinded Phase 1b study with patients diagnosed with recurrent major depressive disorder, NSI-189 exhibited a large effect size (Cohen's $d=0.95$) in MADRS compared to placebo (Fava et al., 2016). It is currently being tested in a Phase 2 efficacy study with MDD patients. Recent preclinical studies suggest NSI-189's potential as a broad neurotrophic agent that may be applicable in treating diverse diseases involving various central and peripheral neurodegenerative conditions.

Learning Objectives:

- NSI-189 illustrates a novel relationship between neurogenesis, hippocampal volume, and depression.
- A common molecular pathway seems to underlie neurogenesis, synaptic plasticity, and neuro-regeneration.

Literature References:

- A Phase 1B, randomized, double blind, placebo controlled, multiple-dose escalation study of NSI-189 phosphate, a neurogenic compound, in depressed patients. Fava, M. et al. *Mol Psychiatry*. 2016 Oct;21(10):1372-80.
- The current state of the neurogenic theory of depression and anxiety. Miller BR and Hen R. *Curr Opin Neurobiol*. 2015 Feb;30:51-8.

THE POTENTIAL THERAPEUTIC ROLE OF ANTI-INFLAMMATORY AGENTS FOR MOOD DISORDERS*

Giacomo Salvatore, Janssen Pharmaceuticals

Individual Abstract: Major Depressive Disorder (MDD) is well known to be a heterogeneous illness, and the approximately one-third of depressed patients who are deemed to be treatment resistant may have distinct mechanisms underlying their depression, including systemic inflammation, resulting in reduced responsiveness to traditional monoamine treatment approaches. For example, Interleukin-6 (IL-6) levels correlate with depression severity in patients who do not respond to conventional antidepressant treatments suggesting that a subset of depressed patients with treatment resistance may have an immune-mediated component to their illness which is evident in the periphery. Similarly, accumulating evidence suggests that dysregulation of the immune system may also be an important contributory factor to the pathophysiology of bipolar disorder as well.

The putative role of dysregulation of the immune system in the pathophysiology of mood disorders is supported by cross-sectional studies and meta-analyses reporting elevation of selected inflammatory markers in the periphery in patients with MDD and bipolar disorder, as well as by the evidence that treatments and experimental challenges which induce a pro-inflammatory state induce depressed mood and other symptoms of depression in susceptible subjects. In addition, preclinical data in animal models of depression show that chronic stress induces elevation of inflammatory markers, such as IL-6 and IL-1 β .

Clinical studies in subjects with MDD and bipolar depression have evaluated the potential antidepressant effects of immune-based therapeutic approaches, such as non-steroidal anti-inflammatory drugs and anti-TNF alpha antibodies; preliminary meta-analyses suggest that decreasing inflammation in subjects with mood disorder may have antidepressant effects; however those meta-analyses also highlight the heterogeneity between studies, the individual low sample size and the lack of an enrichment strategy to identify those subjects with mood disorders with evidence of increased immune activity who may be more prone to respond to such therapeutic approaches. A currently on-going study is testing the hypothesis that IL-6 inhibition through the administration of Sirukumab, a human anti-IL-6 monoclonal antibody, is associated with antidepressant effects in subjects with MDD with suboptimal response to current antidepressant treatment who exhibit elevated levels of C-Reactive Protein (CRP). This presentation will discuss the studies investigating anti-immune treatments as novel antidepressant strategies in subjects with mood disorder, as well as methods and challenges to apply stratified medicine approaches to clinical trials.

Learning Objectives:

- To review the strengths and limitations of the clinical studies which have investigated the potential antidepressant effects of anti-immune therapeutic approaches in subjects with mood disorders.
- To discuss the methodological challenges of conducting clinical trials in subjects with mood disorders and evidence of increased immune activity to investigate the potential antidepressant effects of molecules which inhibit specific cytokines, such as IL-6.

Literature References:

- Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, Krogh J, 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71:1381-91.
- Rosenblat JD, Kakar R, Berk M, Kessing LV, Vinberg M, Baune BT, Mansur RB, Brietzke E, Goldstein BI, McIntyre RS, 2016. Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. *Bipolar Disord* 18:89-101.

SYNAPTIC AND EXTRASYNAPTIC GABA-A RECEPTORS AS DRUG TARGETS IN POSTPARTUM DEPRESSION AND MAJOR DEPRESSIVE DISORDER: DEVELOPMENT OF TWO POSITIVE ALLOSTERIC MODULATORS*

Stephen Kaner, Sage Therapeutics

Individual Abstract: Depression is a common and serious mood disorder and a contributor to global disease burden. First-line antidepressants include monoamine-oxidase inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants, but their efficacy is

often limited in terms of response and remission rates. GABAergic dysfunction has been implicated in the pathophysiology of mood disorders, including postpartum depression (PPD) and major depressive disorder (MDD), which provides an opportunity for potentially developing drugs with novel mechanisms of action. Neuroactive steroids (NASs) can function as positive allosteric modulators (PAM) of synaptic and extrasynaptic GABA-A receptors, and altered levels of NASs have been implicated in depressive disorders. Brexanolone (USAN; formerly SAGE-547 Injection) is a proprietary formulation of the NAS allopregnanolone. The safety, tolerability, pharmacokinetics (PK), and efficacy of brexanolone were initially evaluated in an open-label, proof-of-concept study in severe PPD that supported further investigation of brexanolone in PPD. A subsequent double-blind, randomized, placebo-controlled, Phase 2 study in 21 women with severe PPD showed that brexanolone provided statistically significant and clinically meaningful reductions in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at 24 hours ($p=0.006$) post infusion start and continuing through the primary endpoint of 60 hours ($p=0.008$) with reduction sustained at 30 days ($p=0.01$), relative to placebo. Remission rates (HAM-D ≤ 7) at 60 hours were 70% for brexanolone-treated subjects and 9% for placebo-treated subjects ($p=0.008$), with similar differences maintained through 30 days (70% vs. 18%, respectively; $p=0.030$). Secondary efficacy endpoints were consistent with the HAM-D-based outcomes. Brexanolone was generally well tolerated. The most commonly reported AEs in the brexanolone group were dizziness (2 subjects; 3 placebo-treated subjects) and somnolence (2 subjects; 0 placebo-treated subjects). There were no deaths, serious adverse events, or discontinuations due to adverse events.

SAGE-217 is a next-generation oral NAS with similar pharmacology to brexanolone and a PK profile intended for once daily oral administration. A recently-completed open-label portion (Part A) of a two-part Phase 2a study in subjects with moderate to severe MDD showed generally favorable tolerability and encouraging signals of efficacy. Thirteen subjects received an open-label nightly dose of 30 mg SAGE-217 on Days 1-14, and adverse events and HAM-D scores were assessed through Day 28. There were no deaths, serious adverse events, or discontinuations. The most common AEs were sedation/somnolence, headache, dizziness, and myalgia. The mean baseline HAM-D total score was 27.2. There was a mean reduction from baseline of 19.9 points at Day 15; 85% (11/13) of subjects were responders ($\geq 50\%$ reduction of HAM-D) and 62% (8/13) achieved remission (HAM-D ≤ 7). Statistically significant mean changes from baseline in the HAM-D total score were observed on Day 2 ($p=0.0005$) and maintained through Day 15 ($p=0.0001$).

The initial clinical profiles of these two NAS allosteric modulators – brexanolone and SAGE-217 – suggest that PAM modulation of synaptic and extrasynaptic GABA-A receptors may be an important mechanism of action to target for the development of next-generation antidepressants. Ongoing trials with brexanolone and SAGE-217 include a pivotal study with brexanolone in PPD, as well as randomized, double-blind, placebo-controlled Phase 2 studies of SAGE-217 in PPD and MDD.

Learning Objectives:

- Learn about the potential of neuroactive steroids and positive allosteric modulation of GABA-A receptors in the treatment of depressive disorders.
- Learn about two GABA positive allosteric modulators currently in clinical development for postpartum depression and/or major depressive disorder.

Literature References:

- Modgil A, Parakala ML, Ackley MA, Doherty JJ, Moss SJ, Davies PA: Endogenous and synthetic neuroactive steroids evoke sustained increases in the efficacy of GABAergic inhibition via a protein kinase C-dependent mechanism.
- *Neuropharmacology* 2017; 113: 314–322.
- Kaner SJ, Colquhoun H, Doherty J, Raines S, Hoffmann E, Rubinow DR, Meltzer-Brody S: Open-label, proof-of-concept study of SAGE-547 (allopregnanolone) in the treatment of severe postpartum depression. *Human Psychopharmacology* 2017 (In press).

1:15 p.m. - 1:45 p.m.

NIH Diversity Supplement Program

NIH DIVERSITY SUPPLEMENT SESSION*

Lynn Morin, NIH/NIAAA

Overall Abstract: The National Institutes of Health (NIH) Research Supplements to Promote Diversity in Health-related Research Program, also known as the Diversity Supplement Program provides additional funds to parent awards to improve the diversity of the research workforce by recruiting and supporting students, post-doctorate and eligible investigators from groups that have been shown to be underrepresented in health-related research. This session will offer Investigators the opportunity to learn more about the Program in general and specifics to NIAAA. Current and future student candidates are also encouraged to attend to ask questions regarding their current program, requirements and next steps and learn how this program can help advance their careers.

Learning Objectives:

- Be able to describe the Diversity Supplement program in general; the benefits to underrepresented communities; and the application process.
- Know where to find more information on the program and the various requirements specific to NIAAA for submitting an application.

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

Pharmaceutical Pipelines

A PHASE IB DOSE RANGING STUDY OF DIRECT NOSE TO BRAIN DELIVERY OF NEUROPEPTIDE Y IN PATIENTS WITH POSTTRAUMATIC STRESS DISORDER

*James Murrough*¹, Sehrish Sayed¹, Nicholas Van Dam¹, Sarah Horn¹, Marin Mautz¹, Michael Parides¹, Sara Costi¹, Katherine Collins¹, Dan Iosifescu¹, Aleksander Mathé², Steven Southwick³, Adriana Feder¹, Dennis Charney¹*

¹Icahn School of Medicine at Mount Sinai, ²Karolinska Institutet, ³Yale

Abstract: Background: Anxiety and trauma-related disorders are among the most prevalent and disabling medical conditions in the U.S., and posttraumatic stress disorder (PTSD) in

particular exacts a tremendous public health toll. We examined the tolerability and anxiolytic efficacy of neuropeptide Y (NPY) administered via an intranasal route in patients with PTSD. Methods: This randomized, cross-over, dose-ranging study enrolled 24 individuals according to an escalation algorithm into one of five dose cohorts as follows: 1.4 mg (n=3), 2.8 mg (n=6), 4.6 mg (n=5), 6.8 mg (n=6), and 9.6 mg (n=6). Each individual was dosed with NPY/placebo on separate treatment days one week apart in random order under double-blind conditions; assessments were conducted at baseline and following a trauma script symptom provocation procedure subsequent to dosing. Occurrence of adverse events represented the primary tolerability outcome. The difference between treatment conditions on anxiety as measured by the Beck Anxiety Inventory (BAI) and the State-Trait Anxiety Inventory (STAI) immediately following the trauma script represented the principal efficacy outcomes. Results: NPY was well tolerated up to and including the highest dose. There was a significant interaction between treatment and dose; higher doses of NPY were associated with a greater treatment effect, favoring NPY over placebo on BAI score ($F_{1,20}=4.95$, $p=0.038$). There was no significant interaction for STAI score. Conclusions: These data suggest that intranasal NPY is well tolerated up to 9.6 mg and may be associated with anxiolytic effects. Additional studies exploring the safety and efficacy of NPY are warranted.

LOW-DOSE BEDTIME SUBLINGUAL CYCLOBENZAPRINE (TNX-102 SL*) FOR THE TREATMENT OF MILITARY-RELATED PTSD: RETROSPECTIVE ANALYSES OF THE MEDIATORS AND MODERATORS OF TREATMENT RESPONSE

*Gregory Sullivan*¹, Judith Gendreau¹, Michael Gendreau², Jean Engels³, Ashild Peters¹, Perry Peters¹, Seth Lederman¹*

¹Tonix Pharmaceuticals, Inc., ²Gendreu Consulting, ³Engels Statistical Consulting

Abstract: Background: Study TNX-CY-P201 ('AtEase Study') was a Phase 2 efficacy and safety trial of TNX-102 SL for PTSD in a military-related PTSD sample. TNX-102 SL is a sublingual tablet formulation of low dose cyclobenzaprine designed for bedtime administration and rapid sublingual absorption, which bypasses first-pass metabolism and has desirable parent and major metabolite pharmacokinetic profiles. Cyclobenzaprine, a unique tricyclic molecule, has potent 5-HT_{2A} serotonergic, alpha-1-adrenergic, and H₁-histaminergic receptor blocking properties in receptor binding studies. TNX-102 SL is hypothesized to improve global symptoms of PTSD through therapeutic effects on sleep disturbance and hyperarousal. The analyses to be presented explored moderators and mediators of treatment response to TNX-102 SL.

Methods: AtEase was a 12-week, double-blind, placebo-controlled, randomized multicenter trial in males and females, ages 18-65 years, meeting DSM-5 PTSD diagnosis as assessed by Clinician Administered PTSD Scale for DSM-5 (CAPS-5). Participants were randomized at 24 US sites to TNX 2.8 mg (1 x TNX-102 SL 2.8 mg tablet), TNX 5.6 mg (2 x TNX-102 SL 2.8 mg tablets) or placebo in a 2:1:2 ratio. Eligible participants had experienced Criterion A-qualifying trauma(s) during military service since 2001, had at least moderate PTSD severity (CAPS-5 score ≥ 29), and were free of antidepressants for >2 months and free of or washed off other psychotropics. Exclusions included serious suicide risk, unstable medical illness, substance use disorders within 6 months, and lifetime history of bipolar, psychotic, obsessive-compulsive, or antisocial personality disorders. The primary efficacy analysis was

the mean change from baseline (MCFB) in CAPS-5 score between TNX 2.8 mg and placebo. Secondary analyses included MCFB in CAPS-5 between TNX 5.6 mg and placebo, and group comparisons on the Clinical Global Impression-Improvement scale, Sheehan Disability Scale, PROMIS Sleep Disturbance, and CAPS-5 clusters.

Results: A total of 245 participants were enrolled in 2015. Although the primary efficacy analysis comparing TNX 2.8 mg (n=90) to placebo (n=92) was not significant, the TNX 5.6 mg (n=49) group demonstrated a strong trend towards greater MCFB improvement in CAPS-5 at Week 12 (p=0.053, MMRM; effect size=0.36). Sensitivity analyses showed significantly greater improvement in total CAPS-5 with TNX 5.6 mg compared with placebo.

Improvements in sleep and hyperarousal occurred early (by Week 2) and appeared to mediate therapeutic response. Moderator analyses indicated those with combat trauma subtype (85%) and greater baseline CAPS-5 severity scores were those who responded most robustly to TNX 5.6 mg. The most common adverse event (AE) in the TNX-102 SL arms was tongue numbness (39% in TNX 2.8 mg; 36% in TNX 5.6 mg), which was generally transient (<1 hour), and never rated as severe. Systemic AEs of somnolence, sedation, headache appeared dose-dependent; rates in TNX 5.6 mg were 16%, 12%, 12%, respectively.

Discussion: TNX 5.6 mg demonstrated activity over placebo in this multicenter trial in military-related PTSD, heretofore considered a population difficult to treat with pharmacotherapies. This talk will focus on the retrospective analyses indicating treatment response was mediated by primary effects on sleep and arousal, and that moderators of treatment response included combat trauma subtype and higher CAPS-5 baseline. Discussion will also address how these analyses supported advancement of TNX 5.6 mg to Phase 3 testing for PTSD (the “HONOR Study,” currently ongoing).

Trial Registration

NCT02277704

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

DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE NOVEL THERAPEUTIC AEVI-001 IN ADOLESCENTS WITH ADHD AND GLUTAMATERGIC NETWORK GENE MUTATIONS

*Robert Findling², Colleen Anderson¹, David Fitts¹, Liza Squires¹, Garry Neil^{*1}*

¹Aevi Genomic Medicine, ²Johns Hopkins University and Kennedy Krieger Institute

Abstract: Objective: Loss-of-function mutations (copy number variations, CNVs) in metabotropic glutamate receptors (GRMs) and related genes have been identified in ~20% of children/adolescents with ADHD, representing a population in which glutamatergic dysfunction may play a key role in ADHD pathogenesis. Children/adolescents with mutation-positive ADHD (GRM+ ADHD) may be candidates for glutamate-modulating therapy. We will report results of a Phase 2 study evaluating the efficacy and tolerability of the glutamate modulator AEVI-001 in adolescents with moderate severity GRM+ ADHD.

Methods: Phase 2 randomized, double-blind, placebo-controlled, parallel-group study of 6-week duration in subjects 12-17 yrs of age with moderate severity ADHD (baseline ADHD-RS-5 score: ≥ 28 without conventional ADHD therapy) and GRM biomarker-positive genotype (GRM+ ADHD). All ADHD medications were discontinued with appropriate washout period before randomization. 4-wk dose optimization period: 100-mg b.i.d. starting

**of special interest to clinicians*

dose increased at weekly intervals based on clinical response to maximal dose of 400 mg b.i.d. Optimized dose (100 mg, 200 mg, or 400 mg b.i.d.) was maintained 2 weeks.

Results: 101 subjects were randomized 1:1 to placebo or study drug. Baseline characteristics: male, 63%; median age, 14 yrs; median age at ADHD diagnosis, 6 yrs; median years since ADHD diagnosis, 7 yrs; ADHD presentation: inattentive, 29%; hyperactive/impulsive, 2%; combined, 69%. Median Baseline CGI-S score, 4. Mean Baseline ADHD-RS-5 score, 38 (range 12 – 54). Efficacy and tolerability/safety results to be presented, including primary endpoint (ADHD-RS-5 total score change from Baseline to end of treatment as LOCF analysis) and secondary endpoint (number and percent of subjects “Improved” vs. “Not Improved”). Analyses will also include % patients meeting responder criteria defined as $\geq 30\%$ change from Baseline ADHD-RS-5 or CGI-I score of 1 or 2.

Conclusion: Subject characteristics were consistent with expectations. Efficacy and safety/tolerability results will be presented. Study sponsored by Aevi Genomics Medicine.

SAGE-547 AND SAGE-217: NOVEL POSITIVE ALLOSTERIC MODULATORS OF SYNAPTIC AND EXTRASYNAPTIC GABA-A RECEPTORS BEING INVESTIGATED IN THE TREATMENT OF MOOD DISORDERS

*Stephen Kanés*¹, Helen Colquhoun¹, James Doherty¹, Shane Raines², Ethan Hoffmann¹, David Rubinow³, Samantha Meltzer-Brody⁴, A.J. Robichaud¹*

¹Sage Therapeutics, ²2b Analytics, ³University of North Carolina, ⁴UNC School of Medicine

Abstract: GABA is the primary inhibitory neurotransmitter in the brain and binds to ligand-gated chloride ion channels (GABAA receptors) and G protein-coupled receptors (GABAB receptors). GABAA receptors are present both in the synapse as well as extrasynaptically, and their function can be enhanced by positive allosteric modulators (PAMs) that increase receptor efficacy and/or potency. Nonclinical and clinical evidence suggest the role of GABAergic dysfunction in a variety of disease states, including mood disorders such as postpartum depression (PPD) and major depressive disorder (MDD). In PPD, evidence indicates that rapid, post-childbirth decreases in levels of the endogenous neuroactive steroid (NAS) allopregnanolone, the predominant metabolite of progesterone and a PAM of GABAA receptors, may trigger PPD. In MDD, low GABA and allopregnanolone levels have been found in the brain, cerebrospinal fluid, and plasma of depressed patients, and multiple antidepressant agents have been shown to elevate allopregnanolone levels in animal models and in depressed patients.

SAGE-547 Injection (brexanolone, USAN) is a proprietary formulation of allopregnanolone. The safety, tolerability, pharmacokinetics (PK), and efficacy of SAGE-547 were initially evaluated in an open-label, proof-of-concept study that supported further investigation of SAGE-547 for severe PPD. A subsequent double-blind, randomized, placebo-controlled, Phase 2 study in 21 women with severe PPD showed SAGE-547 provided statistically significant and clinically meaningful reductions in 17-item Hamilton Rating Scale for Depression (HAM-D) total score at 24 hours ($p=0.006$) post infusion start and continuing through the primary endpoint of 60 hours ($p=0.008$) with reduction sustained at 30 days ($p=0.01$), relative to placebo. SAGE-547 was generally well tolerated.

SAGE-217 Oral Solution is a next-generation NAS with similar pharmacology to allopregnanolone and a PK profile optimized for once daily oral administration. SAGE-217 was investigated in Phase 1 single ascending dose (SAD) and multiple ascending dose

(MAD) studies. In the SAD study, 72 healthy volunteers were administered SAGE-217 at doses between 0.25 and 66 mg in 9 double-blind, placebo-controlled cohorts (randomized 6:2). In the MAD study with 36 healthy volunteers, 3 double-blind, placebo-controlled cohorts (randomized 9:3) received morning doses of 15 mg, 30, and 35 mg over 7 days. The 30 mg cohort was also dosed in the evening for another 7 days.

SAGE-217 was generally well tolerated in the SAD and MAD trials. Doses were escalated until the maximum tolerated dose (MTD) was achieved based on pre-specified stopping criteria related to sedation. Electroencephalogram recording was used to assess electrical activity as a surrogate for target engagement (GABAA receptor modulation) and suggested evidence of target engagement starting at the lowest dose. The PK profile obtained in the SAD/MAD studies with SAGE-217 was consistent with once daily, oral dosing, displaying dose linearity over the multiple-dose range studied (15-35 mg) and a half-life ranging from 16-21 hours.

To date, results from clinical trials with SAGE-547 and SAGE-217 support continued development as potential therapies for mood disorders. Ongoing trials include a pivotal study with SAGE-547 in PPD, as well as Phase 2 studies of SAGE-217 in PPD and MDD.

DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF KETAMINE THERAPY IN TREATMENT-RESISTANT DEPRESSION (TRD)

Maurizio Fava^{*1}, *Marlene Freeman*¹, *Martina Flynn*¹, *Heidi Judge*¹, *Bettina Hoepfner*¹, *Cristina Cusin*¹, *Dawn Ionescu*¹, *Sanjay Mathew*², *Lee Chang*², *Dan Iosifescu*³, *James Murrough*³, *Charles Debattista*⁴, *Alan Schatzberg*⁴, *Madhukar Trivedi*⁵, *Manish Jha*⁶, *Gerard Sanacora*⁷, *Samuel Wilkinson*⁸, *George Papakostas*¹

¹*Massachusetts General Hospital*, ²*Baylor College of Medicine*, ³*Icahn School of Medicine at Mount Sinai*, ⁴*Stanford University School of Medicine*, ⁵*UT Southwestern Medical Center*, ⁶*UT Southwestern*, ⁷*Yale Department of Psychiatry*, ⁸*Yale School of Medicine*

Abstract: Over the last two decades, a series of placebo-controlled studies has demonstrated the ability of intravenous ketamine (0.5 mg/Kg infusion), an N-Methyl-D-aspartate (NMDA) antagonist, to provide significant symptom amelioration in treatment-resistant depression (TRD) patients within a few hours, with symptoms typically returning within a period of days after discontinuation of the acute intervention. We wanted to investigate whether this is a dose-response effect of intravenous ketamine in TRD in the three days following the infusion. This was a six-site, double-blind, placebo-controlled study of the acute efficacy of intravenous ketamine or placebo added to ongoing, stable, and adequate antidepressant therapy (ADT) in the treatment of adults with TRD. The study was supported by NIMH through the RAPID contract. Following a washout period, 99 eligible subjects were randomly assigned to one of five arms in a 1:1:1:1:1 fashion: a single intravenous dose of ketamine 0.1 mg/kg (n=18), a single dose of ketamine 0.2 mg/kg (n=20), a single dose of ketamine 0.5 mg/kg (n=22), a single dose of ketamine 1.0 mg/kg (n=20), and a single dose of midazolam 0.045 mg/kg (active placebo) (n=19). The study assessments (HAM-D-6, MADRS, SDQ, PAS, SHAPS, CGI-S and CGI-I) were performed at Days 0, 1, 3 (endpoint), 5, 7, 14, and 30 to assess the safety and efficacy of all doses of ketamine compared to active placebo therapy in TRD patients. The overall group*time interaction effect was significant, with both low- and high-doses of intravenous ketamine being superior to active placebo, in terms of the primary outcome measure, the HAM-D-6, as well as the SDQ. Most of the interaction effect

was due to differences at Day 1. Our results challenge the view that only intravenous doses of 0.5 mg/kg or higher are effective in TRD.

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 6-WEEK STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TAK-063 IN SUBJECTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA

*Thomas A. Macek*¹, Maggie McCue¹, Xinxin Dong¹, Elizabeth Hanson¹, Paul Goldsmith², John Affinito¹, Atul R. Mahableshwarkar¹*

¹Takeda Development Center Americas, Inc., ²Takeda Development Centre Europe Ltd.

Abstract: Current treatments for schizophrenia generally have significant side effects and show limited efficacy across symptom domains. TAK-063 is a novel, potent, and selective inhibitor of phosphodiesterase 10A, an intracellular enzyme selectively expressed in the medium spiny neurons of the striatum. TAK-063 has shown efficacy in animal models of schizophrenia, and was shown to be safe and well tolerated in phase 1 studies of healthy subjects and subjects with stable schizophrenia. This study evaluated the efficacy and safety of 20-mg daily TAK-063 versus placebo in subjects with acutely exacerbated symptoms of schizophrenia. Adults aged 18 to 65 with diagnosed schizophrenia and psychotic symptoms that had exacerbated within 60 days of screening were randomized 1:1 to 6 weeks of placebo or TAK-063 taken once daily at night with food. Dose down-titration was allowed (blinded) to TAK-063 10 mg for intolerability. Subjects were hospitalized for the first 3 weeks and could be discharged afterwards at investigator's discretion. The primary endpoint was the least-squares (LS) mean change from baseline in total PANSS score at week 6. The study was powered (80%) to detect a difference on the total PANSS of 10 points at week 6, with a common standard deviation of 20 points (standardized effect size=0.5). Secondary endpoints included the LS mean changes in Clinical Global Impression-Severity (CGI-S) scale, Clinical Global Impression-Improvement (CGI-I) scale, and PANSS Marder Factor scores at week 6. Of the 164 subjects enrolled (n=81, placebo; n=83, TAK-063), 106 completed the study. With the exception of race, the treatment groups were similar; 43 and 65 black subjects were enrolled in the placebo and TAK-063 groups, respectively. The LS mean change from baseline in total PANSS score at week 6 was approximately -14.1 points in the placebo group and approximately -19.5 points in the TAK-063 group (LS mean difference=-5.46; standard error=3.44; p=.115, effect size=0.308) from the mixed model repeated measures analysis. Secondary endpoints were generally supportive of antipsychotic efficacy. The effects on PANSS positive, negative, and general psychopathology subscales and Marder Factors were generally consistent with the changes in Total PANSS. The change from baseline CGI-S at week 6 was -0.76 points in the placebo group and -1.19 points in the TAK-063 group (LS mean difference=-0.43, standard error=0.202, p=.035, effect size=0.413). Changes in CGI-I score favored TAK-063 (LS mean difference=-0.66, standard error=0.244, p=.007, effect size=0.530). Consistent with phase 1 findings, TAK-063 was safe and well tolerated. The rates of all-cause discontinuation were similar between groups. The number of down-titrations was equivalent in each group (1 each). The most frequent treatment-emergent adverse event (TEAE) was somnolence (2.5% placebo vs. 12.0% TAK-063). Extrapyramidal syndromes (EPS) were reported in 12.3% of subjects in the placebo group and 27.7% in the TAK-063 group. There was no difference from placebo in Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) score. TEAEs of EPS graded as "severe" were reported in 2 subjects receiving 20-mg TAK-063.

While the study did not meet its primary endpoint, the data are generally supportive of potential efficacy in the treatment of schizophrenia. Interpretation of the results is confounded by the lack of dose-ranging and active treatment reference.

SINGLE AND MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND CARDIAC SAFETY OF EXTENDED-RELEASE VILOXAZINE (SPN-812 ER) IN HEALTHY ADULT SUBJECTS

*Erika Roers**, *Toyin Adewole*, *Janet K. Johnson*, *Scott T. Brittain*

Supernus Pharmaceuticals, Inc.

Abstract: Introduction: A novel, once-daily, non-stimulant attention-deficit/hyperactivity disorder (ADHD) treatment, extended-release (ER) viloxazine (SPN-812 ER) is in development. Stimulants such as methylphenidate are the first-line pharmacotherapy for ADHD. However, some ADHD patients cannot take stimulants due to adverse effects or contraindications. Non-stimulants provide an invaluable therapeutic alternative. SPN-812 ER is a structurally distinct, bicyclic norepinephrine reuptake inhibitor, with antagonistic activity observed at 5-HT₇ and 5-HT_{1B} receptors and agonistic activity at 5-HT_{2B} and 5-HT_{2C} receptors. Viloxazine, previously approved as an antidepressant in the EU, has had a comprehensive review of its pharmacological, clinical, and safety profiles, which revealed no major safety concerns. The objectives of the present study were to determine the safety, tolerability, and cardiac effects of single ascending doses and multiple ascending doses of SPN-812 ER in healthy adult subjects.

Methods: This was a single-center, randomized, double-blind, placebo-controlled study. Volunteers were healthy adults, 18-45 years old, non-smokers, with a body mass index of 18–28 kg/m². Eight subjects in each of 7 dose cohorts were randomized in a 3:1 ratio to receive a specified dose of active treatment (SPN-812 ER 300 mg, 600 mg, 900 mg, 1200 mg, 1500 mg, 1800 mg, or 2100 mg) or placebo. Cohorts 1-3 were conducted in parallel. Cohorts 4-7 were dosed sequentially given that the tolerability of the previous dose was demonstrated. Subjects were administered a single dose on Day 1 followed by a 48-hour washout period, then were dosed once daily for 5 consecutive days (Days 3-7: multiple dose phase). Adverse events (AEs) and electrocardiograms (ECGs) were recorded throughout the study.

Results: The safety population included 56 subjects. Baseline characteristics were similar across groups. Twenty-three (41.1%) subjects reported at least one TEAE and 19 (33.9%) subjects reported at least one treatment-related AE determined by the investigator. No serious AEs or deaths were reported. Two subjects (3.6%) during the multiple dosing phase at 2100 mg SPN-812 ER, discontinued due to AEs, vomiting and costochondritis, respectively. The most common TEAEs overall were headache (10 subjects, 17.9%), and dizziness and nausea (6 subjects each, 10.7%). Headache, dizziness, and nausea were also the most common treatment-related AEs. During the single-dose phase, headache, somnolence, and dizziness (3, 4, and 3 subjects, respectively) were the most common AEs; of these 10 subjects, more than half occurred in the two highest dose groups. In the multiple-dose phase, the most common TEAEs were headache, nausea, dizziness and vomiting (6, 4, 3, and 3 subjects, respectively); all the nausea and vomiting and half the headaches occurred in the highest dose group. The majority of TEAEs in both phases were mild. The cardiac concentration-effect modeling data (e.g., placebo-adjusted, baseline-corrected QT interval based on the Fridericia correction method [QTcF]) showed no significant effect of SPN-812 ER on cardiac

repolarization or ECG parameters (demonstrated by the significant negative slope, $p=0.0091$) other than a slight increase in heart rate consistent with the known anticholinergic effect of viloxazine.

Conclusions: SPN-812 ER was safe and well tolerated from 300 to 2100 mg/day as a single dose, and from 300 to 1800 mg/day as multiple doses given once daily for 5 consecutive days.

RATIONALE FOR THE CLINICAL DEVELOPMENT OF ITI-214, A PDE1 INHIBITOR

Robert E Davis, Kimberly Vanover, Lawrence P Wennogle, Peng Li, Gretchen Snyder, Joseph Hendrick, Allen Fienberg, Cedric O'Gorman, Sharon Mates*

Intra-Cellular Therapies, Inc.

Abstract: Background: Enzymes of the PDE1 family are calcium/calmodulin activated cAMP/cGMP hydrolases. Active in stimulated or pathological conditions when intra-cellular calcium levels rise, these enzymes exert little influence on basal cellular cyclic nucleotide levels. Consequently, PDE1 inhibitors function to restore normal signaling for both CNS and non-CNS disorders in pathological states, particularly in those states accompanied by high intracellular calcium levels. PDE1 inhibitors have minimal influence in nonpathological states. Intra-Cellular Therapies has developed a portfolio of PDE1 inhibitors, of which ITI-214 is the most advanced and has completed 4 Phase 1 clinical studies. The mechanism of action of ITI-214 and its activity in animal models suggest therapeutic potential for a variety of CNS and non-CNS diseases.

Methods: ITI-214 has been tested in panels of PDEs, GPCRs, and key enzymes. ITI-214 has been tested in a rodent model of novel object recognition to evaluate cognitive effects. ITI-214 was evaluated behaviorally in the step-down latency test of catalepsy in mice. Anti-parkinsonian effects in mice treated unilaterally with 6-hydroxydopamine (6-OHDA) were evaluated using the cylinder test to assess contralateral limb use in the presence and absence of dopamine replacement. Wakefulness and locomotor activity in mice was measured with telemetry.

Results: With 1000-fold selectivity for PDE1 compared with the next nearest PDE family enzyme, ITI-214 has no significant off-target effects when screened against a panel of 70 key receptors & enzymes. ITI-214 has shown activity in rodent models of motor and non-motor symptoms in Parkinson's disease. ITI-214 was able to reverse haloperidol-induced catalepsy; unlike inhibitors of PDE4 and PDE10 (eg. rolipram and papaverine), ITI-214 did not exacerbate catalepsy induced by dopamine antagonism. ITI-214 was also able to reverse reserpine-induced catalepsy. In mice lesioned unilaterally with 6-OHDA, ITI-214 treatment restored contralateral limb use. In this latter model ITI-214 potentiated subthreshold doses of L-DOPA, suggesting that it could be used clinically to reduce the L-DOPA dose. In lesioned mice receiving chronic L-DOPA, PDE1 inhibitors reduced established dyskinesia. Active versus non-motor deficits of Parkinson's disease, ITI-214 was able to improve memory in the novel object recognition model of memory performance. Analogues of ITI-214 have shown dose dependent increases in wakefulness without effects on general locomotion. Finally, ITI-214 has shown anti-inflammatory effects in a number of animal models.

ITI-214 has been tested in 4 Phase 1 clinical trials. This program included a single rising dose study in normal healthy volunteers, a multiple dose study in which ITI-214 was administered

daily over 14 days to healthy volunteers and patients with stable schizophrenia, a study (conducted in Japan) in which ITI-007 was administered for 7 days at multiple rising oral doses, and a bioequivalence study. In all 4 Phase 1 studies, ITI-214 demonstrated a favorable safety profile and was generally well tolerated in both healthy volunteers and patients with schizophrenia. Pharmacokinetic evaluation indicated once-a-day dosing. Analysis of cerebrospinal fluid concentration in the multiple dose study indicated measurable drug concentration demonstrating ITI-214 crosses the blood brain barrier.

Discussion: ITI-214 represents a novel approach for the treatment of CNS and non-CNS disorders with potential utility in a number of indications including Parkinson's disease (motor and non-motor aspects), cognitive enhancement in schizophrenia, Parkinson's and Alzheimer's disease, ADHD and neuroinflammatory disease.

RESULTS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED, TOLERABILITY STUDY OF KARXT: A NOVEL COMBINATION TARGETING MUSCARINIC ACETYLCHOLINE RECEPTORS USING XANOMELINE WITH TROSPIUM CHLORIDE TO MITIGATE CHOLINERGIC SIDE EFFECTS

*Richard Kavoussi², Andrew Miller¹, Alan Breier³, Stephen Brannan^{*1}*

¹Karuna Pharmaceuticals, ²Neurite Consulting, ³Indiana University

Abstract: Background: Muscarinic receptors, particularly M1 and M4, have long been of therapeutic interest for the treatment of psychosis and cognitive impairment. Xanomeline is a preferential M1 /M4 agonist that in both schizophrenia and Alzheimer's disease has demonstrated efficacy for psychosis, and generated promising data for treating cognitive impairment. However, xanomeline produces peripheral cholinergic side effects (nausea, vomiting, diarrhea, excess sweating and salivation) that led to the discontinuation of its development. KarXT is a novel therapeutic in development which combines xanomeline with trospium chloride, a muscarinic antagonist which does not cross the blood-brain barrier, to mitigate peripheral muscarinic effects to improve the tolerability of xanomeline while maintaining its efficacy profile.

Methods: 70 healthy volunteers participated in a double-blind, parallel group, randomized (1:1) trial of trospium chloride 20 mg BID or placebo added to xanomeline 75 mg TID. The objective of the study was to determine if KarXT produced improved tolerability compared to xanomeline plus placebo. There was a two-day run-in period when subjects received only placebo or trospium followed by 7 days of xanomeline in addition to placebo or trospium. Safety and tolerability were analyzed using spontaneous reports of adverse events including five pre-specified cholinergic adverse events (nausea, vomiting, diarrhea, excessive sweating and salivation), visual analog scales (VAS), and clinician-rated measures.

Results: KarXT (trospium plus xanomeline), as compared to placebo plus xanomeline, reduced the incidence of all spontaneously reported cholinergic adverse events: 34.3% vs. 63.6%, $p=0.016$, respectively. Spontaneous reports of each individual cholinergic adverse event were as follows for KarXT vs placebo plus xanomeline, respectively: nausea (17.1% vs 24.2%), vomiting (5.7% vs 15.2%), diarrhea (5.7% vs 21.2%), excess sweating (20.0% vs 48.5%), and excess salivation (25.7% vs 36.4%). KarXT was well tolerated with no associated serious AE's. During the run-in period, 32% of subjects receiving only placebo reported at least one cholinergic adverse event.

KarXT, as compared to placebo plus xanomeline, had lower mean weekly maximum composite cholinergic VAS scores (2.29 vs. 3.82, $p=0.30$, respectively). Mean VAS scores for individual cholinergic symptoms were consistently lower in the KarXT group. However, due to low self-reported scores on the VAS scales, these measures were not sufficiently sensitive to detect statistical differences between groups.

On the clinician-rated Postoperative Nausea and Vomiting Scale, nausea and vomiting were seen less frequently in the KarXT group compared to the placebo + xanomeline group (14.7% and 2.9% vs. 25.0% and 15.6% respectively). Using the Unified Parkinson's Disease Rating Scale, excess salivation was seen less frequently in the KarXT group (3.2% vs. 16.1%). On the Hyperhidrosis Disease Severity Scale, excess sweating was less common in the KarXT group (3.2% vs. 19.4%).

Conclusions: This KarXT proof-of-concept tolerability study demonstrates that the addition of trospium chloride results in a clinically meaningful improvement in the tolerability of xanomeline. The results described here together with previous efficacy data in schizophrenia and Alzheimer's disease suggests the potential therapeutic utility of KarXT as a novel antipsychotic and procognitive agent. A Phase II, inpatient, double-blind, placebo-controlled, monotherapy trial of KarXT in schizophrenia patients with an acute exacerbation of symptoms is planned.

LONG-TERM EFFICACY AND SAFETY OF EXTENDED-RELEASE MOLINDONE (SPN-810) TO MANAGE IMPULSIVE AGGRESSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Abstract: Background: This study sought to assess overall clinical response during long-term use (up to 6 months) of extended-release molindone (SPN-810), a dopamine D2/D5 receptor antagonist, to manage impulsive aggression (IA) in children 6-12 years old with attention deficit hyperactivity disorder (ADHD) concurrently treated with an FDA-approved dose of a stimulant or atomoxetine.

Methods: Patients who completed the Phase 2B, double-blind (DB), placebo-controlled, dose-ranging study were enrolled in an open-label extension (OLE) in which SPN-810 dosages were adjusted according to clinical response after blinded conversion to 18 mg (<30 kg) or 36 mg (≥ 30 kg). For the DB study, patients had to have ADHD diagnosis and a Retrospective-Modified Overt Aggression Scale (R-MOAS) score ≥ 24 at screening and ≥ 20 after a 3-week OL stimulant optimization period. Key endpoints presented include adverse event (AE) occurrence and change in R-MOAS score.

Results: Of 78 patients entering the OLE, 52 (67%) completed it. Most common reasons for discontinuation were consent withdrawn (11.5%), AEs (9%), lost to follow-up (6%), and investigator decision (4%). Most common AEs considered possibly/definitely related to study medication were sedation (11.5%), increased appetite (9%), weight gain (8%), and somnolence (5%). Treatment-related AEs were dose related (9 mg/day, 13%; 36 mg/day, 33%). Two patients developed symptoms suggestive of extrapyramidal symptoms (dyskinesia, $n=1$; dystonia, $n=1$), which resolved with dose reduction ($n=1$) or with no action taken ($n=1$). Treatment-related AEs resulting in discontinuation ($n=5$) included aggression ($n=2$), weight gain ($n=2$), and tachycardia ($n=1$). There were no notable or systematic effects

on laboratory assessments, vital signs, or ECGs. Median R-MOAS changes from DB baseline were -31.5, -25.0, and -27.0 at OLE maintenance doses of 18, 27, and 36 mg/day, respectively; median R-MOAS changes from OLE baseline were 0, 10, and 0 at OLE maintenance doses of 18, 27, and 36 mg/day, respectively.

Conclusions: Improvements in patients with IA behavior achieved with SPN-810 treatment (R-MOAS change from DB baseline) were sustained during OLE treatment (stable R-MOAS score from OLE baseline). SPN-810 was generally well tolerated, and there was a relatively low rate of discontinuation due to AEs. AEs were consistent with the types of events expected in children receiving low-dose SPN-810 added to ADHD medication.

BREMELANOTIDE (BMT) FOR HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD): EFFICACY ANALYSES FROM THE RECONNECT STUDY

*Anita Clayton*¹, Sheryl Kingsberg², James Simon³, Robert Jordan⁴, Johna Lucas⁴*

¹University of Virginia, ²University Hospitals Case Medical Center, ³Washington University and Women's Health and Research Consultants, ⁴Palatin Technologies, Inc.

Abstract: Background: The most common sexual concern expressed by women is diminished or lack of desire for sexual activity. When accompanied by distress this may be diagnosed as HSDD. BMT's mechanism of action is different from the only approved treatment for HSDD, thus providing an important option.

Objective: The objective of the RECONNECT Study was to evaluate the efficacy of BMT as a treatment for HSDD in premenopausal women.

Material/Method: The RECONNECT study comprises 2 Phase 3, multicenter trials (301, 302) consisting of a 4-week screening period; a Core Phase (4-week at-home placebo period to establish baseline followed by a 24-week randomized, double-blind treatment period); and an ongoing 52 week open-label extension. During the Core Phase participants self-administered BMT (1.75 mg) or placebo subcutaneously using an auto-injector, as-desired, prior to sexual activity. The co-primary endpoints were change in the desire domain of the Female Sexual Function Index (FSFI-D) and the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) score for feeling bothered by low sexual desire (Item 13). Secondary endpoints were change from baseline to end-of-study in the FSFI total, arousal, lubrication, orgasm, and satisfaction scores; FSDS total and bother scores; Women's Index of Treatment Satisfaction (WITS-9) score; self-assessment of benefit, and satisfying sexual event (SSE) items of the Female Sexual Encounter Profile-Revised (FSEP-R).

Results: The primary efficacy population (Modified Intent-to-Treat) comprises 1202 participants; 856 of whom completed the double-blind phase. Participants were: mean age 39 years, mostly white (>80%), with a mean BMI of 28.7 kg/m². The most frequent diagnosis was HSDD with decreased arousal. Both studies met the pre-specified co-primary efficacy endpoints with clinically meaningful results. Compared with those taking placebo, women using BMT had significantly increased scores on the FSFI-D (Study 301: mean change 0.54 vs 0.24; P=0.0002; Study 302: mean change 0.63 vs 0.21; P<0.001) indicating an increase in desire. Scores for item 13 of the FSDS-DAO showed a significant reduction in distress related to low sexual desire for women using BMT compared to placebo (Study 301: Mean change -0.74 vs -0.35; P<0.0001; Study 302: Mean change -0.71 vs -0.42; P=0.0057. On the secondary outcomes, BMT was associated with significant improvements from baseline to EOS in FSFI total, arousal, lubrication, orgasm, and satisfaction domain scores (all P≤0.01),

FSDS total and bother scores (both $P \leq 0.01$), and WITS-9 and self-assessed benefit (both $P < 0.0001$). FSEP-R scores for satisfaction with desire and arousal were significantly improved in Study 301 ($P \leq 0.01$) but only trending toward significance in Study 302. Changes in the number of SSEs were not significantly different from placebo in either study; however, women taking BMT reported a higher percentage of sexual encounters as satisfactory (64.4% vs 50.9% in Study 301 and 64.8% vs 47.3% in Study 302). The most frequent adverse events were nausea, flushing, and headache; most were mild or moderate. BMT's safety profile was consistent with prior experience.

Conclusions: Treatment with BMT is associated with clinically meaningful and statistically significant improvement in desire and a decrease in distress; both hallmark characteristics of HSDD. BMT is an efficacious treatment for key aspects of sexual function — desire, arousal, lubrication, and orgasm, in premenopausal women.

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

Individual Research Reports

Advances in Schizophrenia Treatment and Assessment*

RISK FACTORS FOR SUICIDALITY IN PATIENTS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW, META-ANALYSIS, AND META-REGRESSION*

Fang Yang, The University of Texas Health Science Center at Houston

Ryan Cassidy, Ives Cavalcante Passos

Abstract: Objective: To determine risk factors associated with suicidality in patients with schizophrenia.

Method: We did a meta-analysis and meta-regression of studies comparing schizophrenia patients with and without suicidality by searching PubMed, Web of Science, and Embase for articles published between Jan 1, 1960, and Dec 18, 2016. Studies that assessed suicide ideation, suicide attempt, and suicide were included. From eligible studies, we extracted presence of the risk factor and total number of patients from both groups. We extracted mean and standard deviation if the risk factor was a numeric variable. We did meta-analyses whenever a specific risk factor was available in two or more studies. A random-effects model with restricted maximum-likelihood estimator was used to synthesize the effect size (assessed by odds ratio [OR] for categorical variables and standardized mean difference [SMD] for numeric variables).

Results: 2354 abstracts were identified and 91 studies were included. Poor treatment compliance (OR 3.17; $p < 0.0001$), history of attempted suicide (OR 3.54; $p < 0.0001$), history of depression (OR 3.32; $p = 0.0001$), current delusions (OR 7.83; $p = 0.0005$), current hallucinations (OR 1.93; $p = 0.0359$), hopelessness (OR 5.28; $p = 0.0048$), being male (OR 1.28; $p = 0.0155$), history of tobacco use (OR 1.46; $p = 0.0169$), history of alcohol use (OR 1.30; $p = 0.0313$), being white (OR 4.92; $p = 0.0418$), high IQ (SMD 1.92; $p < 0.0001$), and shorter illness length (SMD 0.08; $p = 0.0151$) were associated with completed suicide. Physical comorbidity (OR 1.53; $p < 0.0001$), history of depression (OR 4.13; $p < 0.0001$), family history of psychiatric illness (OR 1.77; $p < 0.0001$), family history of suicide (OR 2.50; $p < 0.0001$), history of attempted suicide (OR 3.87; $p < 0.0001$), hopelessness (OR 2.17;

p=0.0001), history of alcohol use (OR 1.66; p=0.0001), history of drug use (OR 1.47; p=0.0061), history of tobacco use (OR 1.49; p=0.0022), being white (OR 1.46; p=0.0022), greater number of psychiatric hospitalizations (SMD 1.48; p<0.0001), higher Beck Depression Inventory (BDI) score (SMD 1.72; p<0.0001), and lower age of onset (SMD 0.84; p=0.0087) were associated with suicide attempt. Interestingly, living alone (OR 0.75; p=0.0374) was protective for suicide attempt.

Hamilton Depression Rating Scale score (SMD 2.19; p<0.0001), PANSS general score (SMD 1.87; p<0.0001) and PANSS positive score (SMD 1.30; p=0.0399) were associated with suicidal ideation.

A multiple meta-regression analysis of risk factors for completed suicide found that studies performed in Europe positively associated with history of attempted suicide (b=4.7625, p=0.0405) and total mean age of the sample positively correlated with being male (b=0.0269, p=0.03). A multiple meta-regression analysis of risk factors for attempted suicide found cross-sectional study design positively correlated with history of drug use (b=1.5113, p=0.0446) and age of onset (b=0.631, p=0.0398). Egger's linear regression test revealed a potential publication bias for history of attempted suicide (z=4.1107, p<0.0001), hopelessness (z=2.5614, P=0.0104), history of alcohol use (z = 1.6900, p = 0.0910), white (z = 2.0546, p = 0.0399), and illness length (z=-1.7204, p=0.0854) for completed suicide. It revealed a potential publication bias for history of attempted suicide (z=2.5916, p=0.0096) and number of psychiatric hospitalizations (z=1.9019, p<0.0572) for attempted suicide.

Conclusions: The results will be useful to develop preventive strategies to combat suicide in patients with schizophrenia. Future studies may use the abovementioned risk factors coupled with machine learning techniques to objectively stratify suicidality in patients with schizophrenia.

Learning Objectives:

- Clarify results reported previously regarding the important risk factors associated with suicidality in patients with schizophrenia, comparing these risk factors with those associated with suicidality in patients with bipolar disorder.
- Propose a need to develop consensus on approaches to access suicidality in patients with schizophrenia and other psychiatric diagnoses.

Literature References: 44 references are now included, below are two of the references:

- Hor K, Taylor M: Suicide and schizophrenia: a systematic review of rates and risk factors. *J. Psychopharmacol.* 2010; 24:81–906.
- Oquendo MA, Perez-rodriuez MM, Poh E, Sullivan G, Burke AK, Sublette ME, Mann JJ, Galfalvy H: Life events: a complex role in the timing of suicidal behavior among depressed patients. [Internet]. *Mol. Psychiatry* 2013; 19:1–8

ASSESSING FUNCTIONAL CAPACITY USING THE UCSD PERFORMANCE-BASED SKILLS ASSESSMENT (UPSA-2-VIM) AND THE VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT TOOL (VRFCAT)*

Alexandra Atkins, NeuroCog Trials

Vicki G. Davis, Adam Vaughan, Brian Saxby, Philip Harvey, Meera Narasimhan, Tom Patterson, Richard S.E. Keefe

Abstract: Reliable measurement of functional capacity is critical in assessing the efficacy of treatments for cognitive impairment in a wide range CNS disorders including schizophrenia,

mood disorders, mild cognitive impairment (MCI) and Alzheimer's disease (AD). Despite FDA requirements for functional co-primary endpoints in clinical trials of cognitive enhancing therapies, development and standardization of these functional measures has lagged behind the equally critical cognitive endpoints. In order to optimize signal detection, measures of functional capacity must offer psychometric properties on par with cognitive endpoints. The present research assesses the relative sensitivity and psychometric reliability of two measures of functional capacity, the UCSD Performance-based Skills Assessment (UPSA-2-VIM) and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). Methods: Participants included 158 patients with schizophrenia and 166 healthy controls. Participants completed the VRFCAT, UPSA-2-VIM and the MCCB at Visit 1. The VRFCAT and UPSA-2-VIM were completed again at Visit 2. Alternate forms were used for the VRFCAT at Visit 2. Analyses examined the sensitivity, test-retest reliability, and practice effects associated with each measure.

Results: High test-retest reliability was demonstrated for the VRFCAT in both Patients and Controls (ICCs= 0.81 and 0.65 respectively). Test-retest reliability for the UPSA-2-VIM was also high (ICC= 0.78 for Patients; ICC=0.75 for Controls). Sensitivity to deficits was similar across the two measures (VRFCAT: $d=1.21$, $p<.001$; UPSA-2-VIM: $d=1.16$, $p<.001$), and was consistent with the sensitivity of the MCCB composite ($d=1.22$, $p<.001$). Practice effects were evident for the UPSA-2-VIM ($d=.35$, $p<.001$), but not for the VRFCAT ($-.04$, ns). The UPSA-2-VIM also demonstrated somewhat increased vulnerability to ceiling effects relative to the VRFCAT, with 8 subjects in the Patient Group performing at ceiling at Visit 1, compared to 2 on the VRFCAT.

Discussion: Findings demonstrate sensitivity and psychometric reliability of both the UPSA-2-VIM and the VRFCAT. Selection of which measure is best-suited for a given study will likely depend on the study design and population of interest. Although findings suggest increased utility of the VRFCAT as a repeated measure in schizophrenia, the UPSA-2-VIM may be equally well-suited for populations less vulnerable to ceiling and practice effects (e.g. MCI/AD), or for single visit studies.

Learning Objectives:

- Understand the importance of co-primary measures for functional capacity.
- Appreciate the value of performance-based assessment of functional capacity across conditions.

Literature References:

- Keefe RS, Davis VG, Atkins AS, Vaughan A, Patterson T, Narasimhan M, Harvey PD. Validation of a Computerized test of Functional Capacity. *Schizophr Res.* 2016;175:90-96.
- Patterson TL, Goldman S, McKibbin CL, Hughs T, Jeste DV. UCSD Performance-Based Skills Assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophr Bull.* 2001;27:235-245.

SCHIZOPHRENIA POLYGENIC RISK SCORE PREDICTS ANTIPSYCHOTIC TREATMENT RESPONSE IN PATIENTS WITH FIRST EPISODE PSYCHOSIS*

Jianping Zhang, The Zucker Hillside Hospital

Delbert Robinson, Jin Yu, W. Wolfgang Fleischhacker, Rena Kahn, John Kane, Anil Malhotra, Todd Lencz

Abstract: Background: The genetic basis of antipsychotic drug efficacy is likely polygenic in nature. Genetic risks of schizophrenia may also be related to antipsychotic drug response. The Psychiatric Genomics Consortium (PGC) genome-wide association study (GWAS) provided evidence of association with schizophrenia risk for many single nucleotide polymorphism (SNP) across the genome. The present study examined whether polygenic risk scores (PRS) based on the PGC GWAS are predictive of antipsychotic efficacy in three cohorts of patients with first episode of psychosis.

Methods: Three clinical trial cohorts with genomic data and antipsychotic efficacy data available at baseline and 3-month follow-up were included in the present study. 1) European First Episode Schizophrenia Trial (EUFEST) has 141 first-episode schizophrenia patients (age=25.6±5.2 years; male=60%; all Caucasian). 2) Zucker Hillside Hospital First Episode Schizophrenia Clinical Trial (ZHH-FE) has 77 first-episode schizophrenia patients (age=23.0±4.9 years; male=75%; mixed ethnicity). 3) The clinical trial conducted as part of the Center for Intervention Development and Applied Research at ZHH (CIDAR) has 100 patients with their first episode psychosis (age=21.5±5.1 years; male=75%; mixed ethnicity). DNA was extracted from peripheral lymphocytes and genotyping was performed using the Illumina Omni-1Quad array (EUFEST and ZHH-FE) or Illumina Infinium HumanOmniExpressExome array platform (CIDAR). All genomic data underwent standard quality control procedure. SNP imputation was conducted by IMPUTE2 against the 1000 Genomes and GRCh37/hg19. PRS was computed based on the results of the PGC schizophrenia GWAS using the PRSice software for the three cohorts separately. SNPs with a p-value less or equal to 0.01 in the GWAS were included in the calculation of PRS. Symptom measure was the total score of the Positive and Negative Symptoms Scale (PANSS) for EUFEST or the Brief Psychiatric Rating Scale (BPRS) for ZHH-FE and CIDAR. Hierarchical linear regression was performed on the 3-month symptom score with the PRS as the predictor while controlling for age, sex, and baseline symptom score. Genomic principal component scores were also covaried to control for population stratification for ZHH-FE and CIDAR due to their mixed ethnicity samples. Due to small sample sizes from each study, meta-analytic approach was used to combine the samples using partial correlation coefficient as the effect size measure.

Results: Combining the three cohorts in a meta-analysis, PRS was significantly predictive of 3-month symptom scores, pooled partial $r = 0.165$, $n = 318$, $p = 0.003$. Higher PRS was associated with higher symptom scores at 3-month follow-up, suggestive of less improvement in treatment. Among individual cohorts, PRS significantly predicted 3-month BPRS total scores in the ZHH-FE cohort, $\beta = 0.68$, partial $r = 0.293$, $p = 0.013$, explaining additional 8.1% of total variance. In the EUFEST cohort, the finding was similar, $\beta = 0.19$, partial $r = 0.212$, $p = 0.012$, explaining additional 3.5% of total variance. However, PRS did not significantly predict 3-month symptom scores in the CIDAR cohort, $\beta = -0.013$, partial $r = -0.005$, $p > 0.50$, explaining essentially no additional variance. The overall results remained significant when only European ancestry individuals were included in the analysis.

Conclusion: These findings suggest that polygenic schizophrenia risk scores may also be related to antipsychotic drug response. Patients with higher polygenic risk scores tended to have less improvement with antipsychotic drug treatment. Further analysis is needed to elucidate a more defined genomic profile for antipsychotic drug response.

Learning Objectives:

- To learn how to combine multiple genetic markers to predict drug response.
- To learn how to use polygenic risk scores.

Literature References:

- Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511:421-427.
- Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. *Bioinformatics*. 2015;31:1466-1468.

LUMATEPERONE (ITI-007): LATE STAGE CLINICAL PROGRAM IN SCHIZOPHRENIA*

Cedric O'Gorman, Intra-Cellular Therapies, Inc.

Kimberly E. Vanover, Robert Davis, Steven Glass, Jelena Saillard, Michal Weingart, Sharon Mates

Abstract: Background: Lumateperone is a first-in-class investigational agent in development for schizophrenia, bipolar depression and agitation associated with dementia. Acting synergistically via serotonergic, dopaminergic and glutamatergic systems, it represents a new therapeutic approach for neuropsychiatric disorders. Lumateperone is a potent 5-HT_{2A} receptor antagonist, a mesolimbic/mesocortical dopamine phosphoprotein modulator (DPPM) with activity as a pre-synaptic partial agonist and post-synaptic antagonist at D₂ receptors, a SERT inhibitor and an indirect glutamate enhancer downstream from dopamine D₁ receptor activation and NMDA and AMPA receptor modulation.

Methods: The schizophrenia program includes 3 large, randomized, double-blind, placebo-controlled trials ('005, '301, and '302), two of which included risperidone as an active control ('005 and '302). The primary endpoint was change from baseline on the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo. Efficacy and safety data for ITI-007 60 mg from large, randomized, double-blind, placebo-controlled acute schizophrenia trials were combined for analyses. Safety measures included observed and reported AEs (adverse events), 12-lead ECGs, 3-positional vital sign assessments, lab assessments (hematology, serum chemistry and urinalysis), Barnes Akathisia Rating Scale, Simpson-Angus Rating Scale, Abnormal Involuntary Movement Scale, and the Columbia - Suicide Severity Rating Scale.

Results: In two separate studies ('005 and '301), ITI-007 60 mg met the primary efficacy endpoint. In the '005 trial, ITI-007 60 mg was statistically significantly superior to placebo at Day 28 on improvement on the PANSS total score ($p=0.017$). In the '301 trial, ITI-007 60 mg again was statistically significantly superior to placebo at Day 28 on the PANSS total score ($p=0.022$). ITI-007 60 mg met the key secondary endpoint of statistically significant improvement on the CGI-S in study '301 ($p=0.003$). ITI-007 40 mg also significantly improved CGI-S ($p=0.025$) and both doses significantly improved the PANSS positive symptom subscale scores. In all studies, lumateperone had a motoric, metabolic, and cardiovascular profile similar to placebo. There were no clinically significant differences from placebo on akathisia or EPS rates. Lumateperone was well-tolerated with placebo-like safety and consistently statistically significant and clinically meaningful safety/tolerability advantages over risperidone across all studies. Additional combined safety and efficacy analyses will be presented.

Discussion: ITI-007 represents a novel approach for the treatment of schizophrenia, as it demonstrates a unique pharmacology as well as a differentiating clinical profile. Data from the ongoing, late-stage programs for ITI-007 for the treatment of schizophrenia, bipolar

depression and agitation associated with dementia continue to further characterize ITI-007's novel mechanism of action as well as the potential clinical benefits for patients, in terms of efficacy and safety.

Learning Objectives:

- Understand the unique pharmacological approach of ITI-007 (lumateperone) to the treatment of schizophrenia.
- Receive an update on the clinical program for ITI-007 (lumateperone) in schizophrenia.

Literature References:

- Lieberman JA et al. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. *Biol Psychiatry*. 2016 Jun 15;79(12):952-61.
- Davis RE, Correll CU. ITI-007 in the treatment of schizophrenia: from novel pharmacology to clinical outcomes. *Expert Rev Neurother*. 2016 Jun;16(6):601-14.

Understanding and Optimizing Treatments for Special Populations: Hypersomnolence, Binge Eating Disorder, Pregnant Women With Depression, and Bipolar Depressive Episodes With Psychosis*

TREATMENT OUTCOMES OF ACUTE BIPOLAR DEPRESSIVE EPISODE WITH PSYCHOSIS*

Marco Antonio Caldieraro, Massachusetts General Hospital

Steven Dufour, Louisa Sylvia, Thilo Deckersbach, Andrew Nierenberg

Abstract: Background: The impact of psychosis in the treatment of bipolar depression is remarkably understudied. The primary aim of this study is to compare treatment outcomes of bipolar depressed patients with psychosis to those without psychosis. The secondary aim is to compare the effect of lithium and quetiapine, each with adjunctive personalized treatments (APTs), in those with psychotic symptoms.

Methods: We used prospective data of a comparative effectiveness study of lithium and quetiapine for bipolar disorder (the Bipolar CHOICE study). Individuals meeting the DSM-IV criteria for an acute bipolar depressive episode were eligible for the present study. Severity was assessed by the Bipolar Inventory of Symptoms Scale (BISS) and by the Clinical Global Impression – Bipolar Version (CGI-BP). Mixed models were used to assess the course of symptoms change, and a Cox regression survival analysis was used to compare remission rates longitudinally.

Results: The sample (n=303) was composed mostly of women (60.7%), the mean age was 39.512.1 years, and psychosis was present in 10.6% (n=32) of the depressed participants. Those with psychotic symptoms had higher scores on BISS Overall before (75.2217.6 vs. 54.8616.3; p<0.001) and after (37.1819.7 vs. 26.2718.0; p=0.003) treatment. They also had more severe depression at baseline (BISS depression domain: 29.57.0 vs. 24.98.0, p=0.002) with less marked differences at the end of the study follow up. The CGI-BP yielded similar results. There was no significant difference in the course of symptoms improvement or in the longitudinal remission rates between those with and those without psychosis. There was no significant difference in the treatment outcomes of lithium and quetiapine among those with psychosis.

Conclusion: Bipolar depressive episodes with psychosis are more severe, but present a similar course of improvement when compared to non-psychotic episodes. Lithium can be as effective as quetiapine in the treatment of outpatients presenting bipolar depressive episodes with psychosis.

Learning Objectives:

- Compare treatment response of bipolar depressive episodes with and without psychosis.
- Compare the effect of lithium and quetiapine in the treatment of bipolar depressive episodes with psychosis.

Literature References:

- Ferrari AJ, Stockings E, Khoo J-P, Erskine HE, Degenhardt L, Vos T, Whiteford HA: The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disord* 2016; 18:440–450
- Nierenberg AA, McElroy SL, Friedman ES, Ketter TA, Shelton RC, Deckersbach T, McInnis MG, Bowden CL, Tohen M, Kocsis JH, Calabrese JR, Kinrys G, Bobo WV, Singh V, Kamali M, Kemp D, Brody B, Reilly-Harrington NA, Sylvia LG, Shesler LW, Bernstein EE, Schoenfeld D, Rabideau DJ, Leon AC, Faraone S, Thase ME: Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. *J Clin Psychiatry* 2016; 77:90–99

OPTIMIZING MEDICATION MANAGEMENT FOR PREGNANT WOMEN WITH DEPRESSION*

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Abstract: Purpose: With an incidence of 7.5%, Major Depressive Disorder is one of the most common complications of pregnancy. Not surprisingly, the frequency of antidepressant use at any time during pregnancy increased from 2.5% in 1998 to 8.1% in 2005. However, data to inform dose requirements across the changing physiologic milieu of pregnancy are meager.

Content: The 3 most commonly prescribed SSRIs in pregnancy are sertraline, fluoxetine, and citalopram. In addition to the large inter-individual variability in drug response in non-gravid patients, pregnancy induces alterations in the activity of several cytochrome (CYP) 450 isoenzymes. CYP3A4, 2D6 and 2C9 are increased, and doses of drugs metabolized by these CYPs must be increased to avoid loss of efficacy. In contrast, CYP2C19 activity decreases and dose reductions may be needed to minimize toxicity. Studies of the effect of pregnancy on SSRI plasma concentrations are limited and have been done primarily by our research group, summarized below:

Sertraline. Sertraline is extensively metabolized by the following CYP450 enzymes: major, 2B6; minor, 2C9, 2C19, 2D6, 3A4/5. We examined plasma C/D ratios that were collected at 20, 30, 36 weeks, at delivery, and 2, 4-6 weeks and 3 months after birth in 6 women. The mean concentration/dose (C/D) ratios for sertraline decreased by an average of 60% between 20 weeks and delivery and returned to pre-pregnancy values at 12 weeks after birth. Our team is referred many women whose antidepressant “lost efficacy” around 20 weeks gestation, which is likely due to declining plasma concentrations. The dose must be increased, which captures the previous level of efficacy within a few days to a week.

Fluoxetine. CYP2D6 metabolizes fluoxetine (FLX), 3A4 and 2C9 play a moderate role and 1A2, 2B6, 2C8 and 2C19 contribute. In 17 subjects, we evaluated C/D ratios of FLX and its active metabolite, which decreased in the final trimester of pregnancy and returned to pre-pregnancy levels by 12 weeks postpartum. A significant negative relationship between depression scores drug concentrations was observed, which suggests that lower FLX concentrations resulted in higher depressive symptom levels.

Citalopram. Citalopram (CIT) is a racemic mixture of S- and R-CIT, with only the S-enantiomer having biological activity. Two compounds are marketed (CIT =Celexa and S-CIT=Lexapro). The metabolism is through three CYPs: 2C19, 3A4 and 2D6. We studied 3 pregnant women treated with CIT and 2 with S-CIT. In 4 of 5 subjects, the C/D ratios for these drugs decreased between 20 weeks gestation and delivery.

The collective data suggest that the C/D ratios decrease in the second half and decline even more dramatically in the third trimester. Our team has been awarded NICHD funding to examine the progressive changes in plasma concentrations of SSRI across pregnancy in 200 women. Serial evaluations of depressive and anxiety symptoms and side effects will be obtained to evaluate their association with plasma concentrations at monthly intervals during pregnancy and twice post-birth. We will investigate the impact of genomic variability on inter-individual differences in SSRI dosing, plasma concentrations and pharmacodynamics during pregnancy, with a focus on genes involved in the metabolism and elimination of SSRIs (CYPs), drug transporters responsible for SSRI access to the central nervous system, and genes encoding critical SSRI targets involved in therapeutic efficacy.

Importance. The results will provide evidence to support therapeutic guidelines for the treatment of MDD across pregnancy. When the decision to treat a pregnant woman with an antidepressant is made, clinicians are compelled to provide the highest quality pharmacologic intervention.

Learning Objectives:

- Strategies for monitoring and adjusting the doses of sertraline, fluoxetine and citalopram across pregnancy and in the early postpartum period, with case examples.
- Using knowledge of the CYP metabolic pathways of other antidepressants to evaluate the potential for changes in C/D ratios and dosage adjustment.

Literature References:

- Avram MJ, Stika CS, Rasmussen-Torvik LJ, Ciolino JD, Pinheiro E, George AL, Wisner KL. Rationale and design for an investigation to optimize SSRI antidepressant treatment for pregnant women with depression. *Clin Pharmacol Ther* 2016;100:31-33.
- Sit D, Perel JM, Luther JF, Wisniewski SR, Helsel JC, Wisner KL. Disposition of chiral and racemic fluoxetine and norfluoxetine across childbearing. *J Clin Psychopharmacol* 2010;30(4):381-386.

DASOTRALINE FOR THE TREATMENT OF MODERATE TO SEVERE BINGE EATING DISORDER IN ADULTS: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY*

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Abstract: Background: Binge eating disorder (BED) is the most common eating disorder in the US, with a lifetime prevalence of 3%. Disturbances in reward circuitry have been implicated in its pathogenesis. Dasotraline is a novel and potent dopamine and norepinephrine reuptake inhibitor with slow absorption and a long half-life resulting in stable plasma concentrations over 24 hours with once-daily dosing. This Phase 2/3 study aimed to evaluate the efficacy and safety of flexibly-dosed dasotraline (4, 6, and 8 mg/day) vs placebo in adults with moderate to severe BED over a 12-week period (NCT02564588).

Methods: Key inclusion criteria included moderate to severe BED based on a history of ≥ 2 binge eating days/week for ≥ 6 months prior to screening, and ≥ 3 binge eating days for each of 2 weeks prior to randomization as documented in participant's binge eating diary. Primary endpoint was change from baseline (CFB) in the number of binge eating days/week at Week 12. Key secondary endpoints were: CFB in Clinical Global Impression–Severity (CGI-S) Scale at Week 12; CFB in Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (YBOCS-BE) at Week 12; and the percent of subjects with a 4-week cessation from binge eating prior to Week 12 or end of treatment (EOT). Except for 4-week cessation, the other 3 variables were analyzed using a mixed model for repeated measures (MMRM).

Results: 317 subjects (84% female) were randomized 1:1 and received ≥ 1 dose of study medication (mean age was 38.2 years; mean number of binge eating days/week, 4.25; mean CGI-S score, 4.5; mean BMI, 34.7). The MMRM analysis of CFB at Week 12 in the number of binge days/week yielded a significant mean difference of -0.99 (95% CI: -0.65 to -1.33 ; $p < 0.001$) favoring dasotraline (-3.74 in the dasotraline group vs -2.75 in the placebo group). All 3 key secondary endpoints were met at Week 12 or EOT: 46.5% of subjects in the dasotraline group achieved at least 4 consecutive weeks' cessation from binge eating vs 20.6% in the placebo group ($p < 0.001$); CFB in CGI-S as well as YBOCS-BE scores were also statistically significant favoring dasotraline over placebo ($p < 0.001$). The treatment-emergent adverse events (AEs) that occurred more frequently with dasotraline vs placebo at $> 2\%$ incidence included: insomnia (44.6% vs 8.1%), dry mouth (27.4% vs 5.0%), decreased appetite (19.7% vs 6.9%), anxiety (17.8% vs 2.5%), nausea (12.7% vs 6.9%) and decreased weight (12.1% vs 0%). Discontinuation due to AEs occurred in 11.5% with dasotraline vs 2.5% with placebo. Conclusions: In adults with moderate to severe BED, dasotraline showed significant and clinically meaningful reductions vs placebo in the frequency of binge eating; global severity of illness; and obsessive-compulsive symptoms related to binge eating. These results suggest dasotraline may offer a novel, well-tolerated and efficacious treatment for BED.

Learning Objectives:

- For readers to become familiar with the efficacy profile of dasotraline in adults with binge-eating disorder.
- For readers to become familiar with the safety profile of dasotraline in adults with binge-eating disorder.

Literature References:

- Koblan KS, Hopkins SC, Sarma K, Jin F, Goldman R, Kollins SH, Loebel A. Dasotraline for the treatment of attention-deficit/hyperactivity disorder: A randomized, double-blind, placebo-controlled proof-of-concept trial in adults. *Neuropsychopharmacology* 2015;40:2745–2752
- Hopkins SC, Sunkaraneni S, Skende E, Hing J, Passarell JA, Loebel A, Koblan KS. Pharmacokinetics and exposure-response relationships of dasotraline in the treatment

THE PREVALENCE AND CORRELATES OF HYPERSOMNOLENCE AND ASSOCIATED ROLE IMPAIRMENT IN THE NATIONAL CO-MORBIDITY SURVEY REPLICATION (NCS-R)*

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Abstract: Introduction: The prevalence and associated socio-demographic characteristics of hypersomnolence in the U.S. are not well studied. In addition, its comorbidity with insomnia and relationship with psychiatric, alcohol and drug use disorders, use of prescription medications and impact on functional impairment is poorly delineated.

Methods: The National Comorbidity Survey Replication (NCS-R) is a nationally representative community household survey of individuals ≥ 18 years. As part of this survey, subjects (n=5,962) were queried about their sleep in the NCS-R Part II questionnaire. Socio-demographic characteristics and prescription medication use were assessed. Subjects were administered the WHO Composite International Diagnostic Interview (WHO-CIDI) to determine various DSM-IV diagnoses and the WHO Disability Assessment Schedule 2.0 (WHO-DAS II) to evaluate for functional impairment. The prevalence of 12-month hypersomnolence, defined per DSM-5 as a subjective sense of sleepiness during the daytime associated with lapses into sleep, not feeling rested despite getting adequate sleep, or having difficulty waking in the morning, was determined. Odds ratios were used to assess associations with various socio-demographic characteristics, insomnia, DSM-IV diagnoses, prescription medication use, alcohol and drug abuse/dependence as well as functional impairment.

Results: The prevalence of hypersomnolence in U.S. adults was 23.34% (SE=0.88). Tetrachoric correlations among constituent symptoms were high (0.56 to 0.97; all $p < 0.05$). Among socio-demographic characteristics, being female (OR=1.41; 95% CI:1.20-1.61), ≤ 45 years (OR=1.35; 95% CI:1.10-1.66), having a low/low-average family income (OR=1.36; 95% CI:1.13-1.65) and being unemployed (OR=1.38; 95% CI:1.11-1.70) were associated with a higher risk of hypersomnolence. Insomnia (OR=5.65; 95% CI:4.55-7.02), DSM-IV anxiety disorders (OR=2.78; 95% CI:2.34-3.31), mood disorders (OR=2.72; 95% CI:2.18-3.39), conduct and oppositional disorders (OR=2.11; 95% CI:1.52-2.93), and substance use disorders (OR=1.56; 95% CI:1.27-1.91) were significantly comorbid with hypersomnolence after accounting for socio-demographic characteristics and other DSM-IV diagnoses. Hypersomnolence was significantly associated with functional impairment (OR=2.01; 95% CI:1.30-3.12). Respondents with hypersomnolence were more likely to report using antidepressants (OR=1.77; 95% CI:1.43-2.19), benzodiazepines (OR=1.50; 95% CI:1.15-1.95) and buspirone (OR=2.78; 95% CI:1.46-5.27).

Conclusion: Hypersomnolence is common in the general population, especially in younger, female, lower income and unemployed subgroups. Hypersomnolence is comorbid with multiple psychiatric and substance use disorders, particularly insomnia, anxiety and depression, as well as antidepressant and benzodiazepine use. Finally, hypersomnolence is associated with significant functional impairment.

Learning Objectives:

- Recognize the common and transdiagnostic nature of hypersomnolence symptoms.
- Acknowledge significant co-morbidity between insomnia and hypersomnolence symptoms.

Literature References:

- Ohayon MM, Dauvilliers Y, Reynolds CF, 3rd. Operational definitions and algorithms for excessive sleepiness in the general population: implications for DSM-5 nosology. *Arch Gen Psychiatry*. 2012;69:71-79.
- Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, Nissen C. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev*. 2010;14:19-31.

Focus on Neurocognition, Neurodegeneration, and Alcohol Misuse*

TRAUMA EXPOSURE MODERATES THE GENETIC OVERLAP BETWEEN ALCOHOL MISUSE AND BIPOLAR DISORDERS IN US ARMY SOLDIERS*

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Abstract: Exposure to traumatic events has many negative consequences related to physical and mental health, including increased risk of substance abuse and other psychiatric disorders. From a molecular point of view, there are likely to be a variety of mechanisms by which trauma exposure affects genome regulation. To date, only single gene interactions for substance use disorders have been reported. However, there is no evidence of trauma-exposure effects across the human genome. To investigate whether trauma exposure moderates the genetic correlation between substance use disorders and psychiatric disorders, we tested whether trauma exposure modifies the association of genetic risks for mental disorders with alcohol misuse and nicotine dependence (ND) symptoms. High-resolution polygenic risk scores (PRS) were calculated for 10,732 US Army soldiers (8,346 trauma-exposed and 2,386 trauma-unexposed) on the basis of the summary statistics obtained from large genome-wide association studies of bipolar disorders (BD), major depressive disorder (MDD), and schizophrenia. The main finding is a Bonferroni-corrected significant PRS-by-trauma interaction for BD PRS with respect to alcohol misuse ($p = 6.07 \times 10^{-3}$). Specifically, we observed a positive correlation between BD PRS and alcohol misuse in trauma-exposed soldiers ($r = 0.029$, $p = 7.5 \times 10^{-3}$) and a negative correlation in trauma-unexposed soldiers ($r = -0.071$, $p = 5.61 \times 10^{-4}$). The variants included in the BD PRS with gene-by-trauma interaction direction for alcohol misuse concordant with PRS-by-trauma interaction showed significant enrichments for gene ontologies related to high voltage-gated calcium channel activity (GO:0008331, $p = 1.51 \times 10^{-5}$; GO:1990454, $p = 4.49 \times 10^{-6}$; GO:0030315, $p = 2.07 \times 10^{-6}$) and for Beta1/Beta2 adrenergic receptor signaling pathways ($p = 2.61 \times 10^{-4}$). Among the variants included in the significant BD PRS, AKAP13 rs12902447 showed a trauma-exposure interaction with respect to alcohol misuse that survived multiple-testing correction ($p = 3.31 \times 10^{-3}$, false discovery rate < 0.1). For ND symptoms, no PRS-by-trauma interaction survived Bonferroni correction. However, we observed a nominally significant PRS-by-trauma interaction ($p = 0.034$), where MDD PRS showed a Bonferroni-corrected significant positive correlation with ND symptoms in trauma-exposed soldiers ($r = 0.041$, $p =$

3.18*10-3). This study provides the first evidence regarding how exposure to traumatic events affects the phenotypic expression of human variation on a genome-wide basis (that is, a set of markers distributed throughout the genome selected for a putative association to a specific psychiatric trait). Our results indicate that the genetic overlap between alcohol misuse and BD is significantly moderated by trauma exposure. This provides molecular insight into the complex mechanisms that link substance abuse, psychiatric disorders, and trauma exposure. Increased knowledge regarding how genetic predisposition and trauma exposure interact to determine respect to substance use behaviors can help to design effective preventive treatments, especially for high-risk people such as military personnel.

Learning Objectives:

- To determine whether exposure to traumatic events affects the phenotypic expression of variation across the human genome.
- To identify the mechanisms by which exposure to traumatic events affects the genetic overlap between substance use disorders and psychiatric disorders.

Literature References:

- Polimanti R, Chen CY, Ursano RJ, Heeringa SG, Jain S, Kessler RC, Nock MK, Smoller JW, Sun X, Gelernter J, Stein MB. Cross-Phenotype Polygenic Risk Score Analysis of Persistent Post-Concussive Symptoms in U.S. Army Soldiers with Deployment-Acquired Traumatic Brain Injury. *J Neurotrauma* 2016; doi: 10.1089/neu.2016.4550.
- Polimanti R, Kaufman J, Zhang H, Kranzler HR, Ursano RJ, Kessler RC, Gelernter J, Stein MB. A genome-wide gene-by-trauma interaction study of alcohol misuse in two independent cohorts identifies PRKG1 as a risk locus. *Mol Psychiatry* 2017; In Press.

THE RELATIONSHIP BETWEEN COGNITIVE AND FUNCTIONAL PERFORMANCE AND MEASURES OF NEURODEGENERATION AMONG HISPANIC AND WHITE NON-HISPANIC INDIVIDUALS WITH NORMAL COGNITION, MILD COGNITIVE IMPAIRMENT, AND DEMENTIA*

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Abstract: Objective: To determine the presence and severity of cultural and language bias in widely-used cognitive and functional measures, using structural MRI measures of neurodegeneration as unbiased biomarkers of disease stage and severity.

Methods: Hispanic (n=82) and White non-Hispanic (WNH) (n=97) subjects were classified as cognitively normal (CN), amnesic MCI (aMCI), and mild dementia. Performance on the culture fair Fuld Object Memory Test (Fuld) and Clinical Dementia Rating Scale (CDR) between Hispanics and WNHs was equivalent, in each diagnostic group. volumetric and visually rated measures of hippocampal, entorhinal cortex, and inferior lateral ventricle (ILV) were measured on structural MRI scans for all subjects. A series of ANOVAs, controlling for age, depression, and education, were conducted to compare the level of neurodegeneration on these MRI measures between Hispanics and WNHs in each diagnostic group.

Results: Among both Hispanics and WNHs there was a progressive decrease in volume of the hippocampus and entorhinal cortex, and an increase in volume of the ILV (indicating increasing atrophy in the regions surrounding the ILV) from CN to aMCI to mild dementia.

For equivalent levels of performance on the Fuld and CDR, WNHs had greater levels of neurodegeneration than Hispanics, as indicated by the MRI measures.

Conclusions: The severity of neurodegeneration, quantified by MRI measures of regional brain atrophy, was more severe among WNHs than Hispanics. This occurred despite similar cognitive and functional performance between the ethnic/cultural groups, using validated tests which are considered unbiased. These findings suggest that certain unmeasured factors resulted in better than expected performance on cognitive and functional measures in the WNH group, which had more severe neurodegeneration compared to the Hispanic group.

Learning Objectives:

- Participants will be able to describe how cognitive tests of memory, executive function, and overall cognitive performance may demonstrate different outcomes by ethnicity / first language even when controlling for factors such as age, sex, education, and socioeconomic status.
- Participants will be able to describe methods of using MRI-based biomarkers to examine concordance and discordance between the reported outcomes of cognitive tests and volumes of individual brain regions.

Literature References:

- Guerrero-Berroa E, Kluger A, Schmeidler J, Sailor K, Lizardi H, Golomb J, Ferris S, Reisberg B. Neuropsychological and Neuropsychiatric Prediction of Global Cognitive Status Among Older Spanish-Speaking Hispanics and English-Speaking Whites. *J. Geriatr. Psychiatry Neurol* 2014; 27(4): 266-275
- Zahodne L, Manly J, Narkhede A, Griffith E, DeCarli C, Schupf N, Mayeux R, Brickman A. Structural MRI predictors of late-life cognition differ across African Americans, Hispanics, and Whites. *Curr Alzheimer Res* 2015; 12(7):632-9.

HAZARDOUS ALCOHOL INTAKE ALTERS BRAIN, AUTONOMIC AND HYPOTHALAMIC-PITUITARY-ADRENAL AXIS RESPONSES TO STRESS*

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Rajita Sinha, Cheryl Lacadie

Abstract: Alcoholism have been associated with altered ventromedial prefrontal cortex (VmpFC) response to stress, increased basal heart rate and blunted cortisol levels.^{1,2} Yet, comprehensive underlying mechanisms linking heavy alcohol use and effects on brain, autonomic nervous system (ANS), and hypothalamic–pituitary–adrenal (HPA) axis activity remain unclear. To understand the alcohol effects on brain and peripheral stress system markers, we present data from two study samples using functional magnetic resonance imaging (fMRI) during brief provocation of stress, alcohol cue, and neutral cues, using a well-validated, individualized imagery paradigm in studies of stress and addiction.

In study 1, we examined neural correlates of ANS activity indexed by heart rate response in 48 social drinkers (age mean=28.31(SD=6.9)) with demographically-matched 26 heavy/binge drinkers (HD) and 22 light drinkers (LD). fMRI images were obtained using a 3T Siemens Trio MRI, and heart rate was collected using a pulse oximeter. Greater basal heart rate and stress-induced alcohol craving ($p < 0.05$) were found in HD compared with LD. fMRI results showed that greater basal heart rate was associated with hypoactive VmpFC ($r = -.52$), but hyperactive medulla oblongata response ($r = .39$), a modulator of ANS system, in all subjects (whole-brain corrected at 0.05), with an inverse association between the VmpFC and medulla oblongata ($r = -.45$; $p = 0.001$). Connectivity results with the medulla as a seed region showed

significant group differences. HD exhibited reduced functional connectivity between the VmPFC and medulla oblongata. Relative to LD, the VmPFC in HD was more disconnected with the medulla during stress. Notably, individuals with reduced connectivity between the VmPFC and medulla had greater amount of alcohol consumption during a laboratory alcohol taste test ($r=-.53$, $p<0.001$) and greater weekly alcohol consumption measured by Calahan index ($r=-.44$, $p<0.01$). In study 2 with 73 healthy individuals (age mean=28.84(SD=8.9)), we investigated the relationship between life trauma on cortisol and fMRI responses to stress using the individualized script-driven imagery method. Greater life trauma scores were associated with blunted basal cortisol levels ($p<0.01$) and stress-induced hyperactivity in limbic-temporal regions including amygdala, hippocampus and medial temporal lobe ($p<0.05$, whole-brain corrected). Blunted basal cortisol levels were also correlated with increased stress-induced activity in the hypothalamus and limbic-temporal regions ($p<0.05$, whole-brain corrected). Connectivity analysis showed the presence of functional connectivity between the hypothalamus and amygdala and VmPFC. Individuals who had weaker connectivity between the hypothalamus and VmPFC consumed greater amount of alcohol measured by Calahan ($r=-.25$, $p<0.05$). The VmPFC regulates emotion, ANS and HPA axis system response especially during stress. Compromised VmPFC regulatory control over HPA and ANS functions may impair adaptive coping behaviors, increasing reward-oriented maladaptive behaviors including risky alcohol use. The integrity of the VmPFC is crucial in modulating adaptive HPA and ANS responses, stress-resilient coping and vulnerability to alcoholism.

(Supported by K08-AA023545; R01-AA013892; UL1-DE019586).

Learning Objectives:

- To review neural markers underlying stress and alcoholism using multimodal methods involving brain, autonomic nervous system (ANS), and hypothalamic–pituitary–adrenal (HPA) axis system.
- To discuss an integrative model of stress and alcoholism linking evidences from brain, ANS, and HPA axis system responses and to discuss a major regulator of this model, the ventromedial prefrontal cortex.

Literature References:

- Seo D, Sinha R. Neuroplasticity and Predictors of Alcohol Recovery. *Alcohol Res.* 2015; 37(1):143-52.
- Seo D et al. Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry.* 2013; 70(7):727-39.

THE IMPACT OF CEREBRAL SMALL VESSEL DISEASE IN ALZHEIMER'S DISEASE AND OTHER LATE LIFE NEUROCOGNITIVE DISORDERS*

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Abstract: Purpose: White matter hyperintensities (WMH) are a neuroimaging marker of brain frailty presumed to indicate damage to the small cerebral blood vessels. We explore how WMH contribute to the presentation of Alzheimer's disease and other neurocognitive

disorders. In particular, we examine relationships with neurocognition and peripheral inflammatory biomarkers that are often elevated in Alzheimer's disease (1). Inflammation contributes to cognitive decline, but it has yet to be correlated with neuroimaging markers in Alzheimer's disease.

Content: We present results from two unique cohorts; one carefully selected to represent the strata of extensive and minimal WMH, both with (n=23) and without (n=44) Alzheimer's disease, and the other a large real-world consecutive case series (n=702) presenting to a cognitive neurology clinic diagnosed with prevailing consensus criteria for the common dementias, without excluding those with small vessel disease.

Methodology: Volumes and microstructural characteristics of WMH were studied using multimodal structural MRI, including diffusion tensor imaging. Peripheral inflammatory markers were assayed using multiplex magnetic bead assays. Cognition was assessed using a standardized cognitive battery, including the California Verbal Learning Test to assess verbal memory. Analyses included correlational statistics, and structural equation modeling techniques to generate composite biomarker scores and to model indirect effects of imaging and peripheral blood markers on cognition.

Results: We confirm known effects of WMH on multiple cognitive domains, including executive function and psychomotor processing speed. We identify a strong relationship between WMH and brain atrophy, and we further show that WMH affect verbal memory performance via an indirect pathway mediated by temporal lobe atrophy. In a subsample of participants, we identify a peripheral immune signature (2) consisting of 5 cytokines, including tumor necrosis factor, interleukin[IL]-1 beta and IL-23, that is related to microstructural damage within periventricular WMH in participants with Alzheimer's disease but not in those without Alzheimer's disease. This inflammatory signature was also related to poorer executive function and poorer verbal memory performance specifically in participants with Alzheimer's disease.

Importance: WMH contribute to pathological heterogeneity across late-life neurocognitive disorders, and they contribute to temporal lobe atrophy, which contributes to the sensitive and specific core cognitive features of Alzheimer's disease. WMH not only map onto cognition, but also onto peripheral inflammatory markers in AD, shedding new light on this perplexing aspect of AD phenomenology and how it may contribute to cognitive symptoms. We discuss how trials evaluating preventative or disease-modifying therapies for Alzheimer's disease, including novel anti-inflammatory agents, might consider this important source of heterogeneity when identifying participants, therapeutic strategies, and outcome measures.

Learning Objectives:

- Appreciate that cerebral small vessel disease is common in Alzheimer's disease, and that it can contribute to cognitive symptoms including memory deficits.
- Appreciate that elevated peripheral inflammatory markers may be related to cerebrovascular damage in Alzheimer's disease.

Literature References:

- Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry*. 2010;68:930-941.
- Swardfager W, Yu D, Ramirez J, Cogo-Moreira H, Szilagyi G, Holmes MF, Scott CJM, Scola G, Chan PC, Chen J, Chan P, Sahlas DJ, Herrmann N, Lanctôt KL, Andreatza AC, Pettersen JA, Black SE. Peripheral inflammatory markers indicate microstructural damage within periventricular white matter hyperintensities in

Treatment Adherence to Atypical Antipsychotic Medications, Ketamine, and Screening for Psychiatric Disorders*

DIFFERENTIAL ADHERENCE TO ANTIPSYCHOTIC MEDICATION IMPACTS CLINICAL AND FUNCTIONAL OUTCOMES IN ANTIPSYCHOTIC-NAÏVE FIRST-EPIISODE PSYCHOSIS PATIENTS: A LONGITUDINAL STUDY*

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Abstract: Background: Adherence to antipsychotic medication, especially at first onset, in psychosis is known to predict better outcomes, including symptomatology and daily functioning. Nevertheless, individuals experiencing psychosis often struggle with remaining adherent to their antipsychotics. Variable adherence may impact outcomes differently and can be a significant barrier to developing more effective treatments. The purpose of this investigation was to examine the effects of differential antipsychotic adherence on clinical and functional outcomes in a unique sample of first-episode psychosis patients naïve to antipsychotics at study entry.

Methods: A total of 223 inpatients and outpatients experiencing first-episode psychosis were consecutively enrolled in a one year naturalistic follow-up study and assessed with clinical and functional measures at baseline, 4-weeks, 6-months, and 1-year. Antipsychotic adherence was defined by categorizing three common patterns of adherence across the three time points following baseline: never, variably, and consistently adherent. Clinical measures included the SAPS, SANS, BPRS, and the Hamilton Rating Scale for Depression. Functional outcome was assessed with the GAF and the Strauss–Carpenter Outcome Scale (SCOS). Linear mixed-effects intent-to-study models were used to examine the impact of differential adherence on outcomes across these three groups.

Results: Differential adherence to antipsychotic medication significantly moderated improvements in positive symptoms ($F(2,535) = 4.46, p = .012$), such that SAPS total item scores were significantly more improved among patients both variably ($t(535) = -2.08, p = .038$) and consistently ($t(535) = -2.99, p = .003$) adherent when compared to those who were never adherent. Adherence also significantly moderated change in general psychopathology, $F(2,535) = 4.46, p = .012$. Patients who were consistently adherent had experienced a greater reduction in BPRS total scores than those who were never adherent ($t(525) = -2.59, p = .010$). Adherence also significantly impacted the rate of improvement in depression scores, $F(2,491) = 3.31, p = .037$. Change in negative symptoms was not significantly related to differential adherence (SANS; $p = .696$). With regard to functioning, adherence moderated improved SCOS scores ($F(2,79) = 2.51, p = .088$), particularly for those who were consistently adherent ($t(79) = 2.18, p = .032$). Change in GAF scores was not significantly predicted by adherence ($p = .399$).

Conclusions: Antipsychotic medication adherence is an important predictor of positive symptom, depressive symptom, general psychopathology, and functional outcome improvements. Given that the first-episode patients who were consistently adherent displayed

the greatest degree of improvement, these findings are supportive of future research efforts aimed at increasing antipsychotic medication adherence and acceptability at first onset.

Learning Objectives:

- Differential adherence to antipsychotic medications at first onset of psychosis may significantly impact long-term outcomes (e.g., one year).
- Exposure to antipsychotic medication is predictive of better symptomatology, excluding negative symptoms, and functional outcomes.

Literature References:

- Coldham EL, Addington J, Addington D: Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatr Scand* 2002;106(4):286-290.
- Malla AK, Norman RM, Manchanda R, Townsend L: Symptoms, cognition, treatment adherence and functional outcome in first-episode psychosis. *Psychol Med* 2002;32(06):1109-1119.

A WEB-BASED SURVEY OF THE CLINICAL, OFF-LABEL USE OF KETAMINE AS A TREATMENT FOR PSYCHIATRIC DISORDERS*

Samuel Wilkinson, Yale School of Medicine

Mesut Toprak, Mason Turner, Steven Levine, Rachel Katz, Gerard Sanacora

Abstract: Introduction: Despite a lack of long-term data or FDA indication, many community providers and academic centers have begun offering ketamine treatment to patients with major depressive disorder (MDD) and other psychiatric disorders. The practice patterns of such providers have not been studied.

Methods: From September 2016 through January 2017, a web-based survey was sent to physicians nationwide inquiring about their clinical practices using ketamine for psychiatric disorders. Physicians were identified through a systematic search.

Results: Survey requests were sent to 76 providers and responses were received from 57 (75.0%). Most (73.7%) survey respondents worked in private practice, with a minority in academic settings (14.0%) or Health Maintenance Organizations (8.8%). Most (66.7%) providers were trained in psychiatry, with others trained in anesthesiology (22.8%), emergency medicine (3.5%), family medicine (3.5%), neurology (1.8%), and physical medicine/rehabilitation (1.8%). Most providers (73.7%) administered ketamine in an office-based setting, with a minority (21.1%) administering ketamine in a hospital-based setting or surgical/procedural suite. The majority of practitioners reported starting to provide ketamine for psychiatric disorders relatively recently, with a drastic increase in cumulative number of providers since 2012. In 2012, there were 14 total ketamine providers; in 2014 there were 21, in 2015 there were 32, and in 2016 there were 57. By conservative estimates, at least 3,670 patients have been treated with ketamine for the treatment of psychiatric disorders. Most providers (87.7%) reported administering ketamine via an intravenous route, with a minority reporting using an oral (22.8%) or an intranasal (19.3%) formulation. Among providers reporting intravenous administration, 44.0% reported using a dose of 0.5mg/kg infused over 40-45 min, the typical dose in most research protocols; a minority reported using a range of doses between 0.5-1.0mg/kg (12.0%) or between 0.5-3.0mg/kg (14.0%). Most providers (89.5%) reported offering ketamine on a continuation/maintenance basis (defined as a time period greater than 1 month). Providers reported the average frequency of maintenance

treatments as monthly (29.8%), once per 3 weeks (21.1%), once per 2 weeks (12.3%), or less than monthly (15.8%).

Conclusion: This is the first attempt to characterize practice patterns among physicians providing ketamine outside of research protocols as a treatment for psychiatric disorders. We identified a rapidly growing number of physicians of a variety of specialties and geographic locations offering ketamine treatment for psychiatric disorders. Various dosing protocols were reported, though the majority of research studies have only used one protocol. These results underscore the urgent need for more research on ketamine use in psychiatric disorders to establish evidence-based treatment regimens and the safety of long-term use. The growing use of ketamine in this population coupled with the concern for potential adverse clinical consequences of repeated dosing (abuse liability, cognitive impairment) argue for the importance of a registry to follow psychiatric patients who receive ketamine longitudinally.

Learning Objectives:

- Recognize the growing trend in the off-label use of ketamine outside research protocols as a treatment for psychiatric disorders.
- Recognize that providers from a variety of different specialties are using a variety of different dosing protocols.

Literature References:

- Sanacora G, Heimer H, Hartman D, Mathew SJ, Frye M, Nemeroff C, Robinson Beale R: Balancing the Promise and Risks of Ketamine Treatment for Mood Disorders. *Neuropsychopharmacology* 2016; doi: 10.1038/npp.2016.193 [Epub ahead of print].
- Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB. Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression: *Am J Psychiatry* 2015;172(10):950-966.

SCREENING FOR PSYCHIATRIC DISORDERS WITH SELF-ADMINISTERED QUESTIONNAIRES*

Mark Zimmerman, Brown University

Caroline Guzman Holst

Abstract: Background: Taking a thorough, comprehensive, history is time consuming. Given the time demands of clinical practice it is not surprising that diagnoses are sometimes missed. To improve diagnostic recognition, self-administered screening scales have been recommended. A problem with much of the research efforts on screening scales is the confusion between diagnostic testing and screening. A diagnostic test is intended to improve diagnostic accuracy and reduce misdiagnosis whereas a screening test is intended to reduce missed diagnoses. It is important for a screening test to have high sensitivity because the more time intensive/expensive follow-up diagnostic inquiry will presumably only occur in patients who are positive on the initial screen. Studies vary in how they analyze their data in determining the cutoff score on a self-administered screening questionnaire. In the present report, we examined how often each of the different approaches towards determining a cutoff score on bipolar disorder screening scales were used.

Methods: We reviewed 68 studies examining the performance of the 3 most commonly researched bipolar disorder screening scales to determine how the recommended cutoff on the scale was derived.

Results: Most studies recommended a cutoff point on the screening scale that optimized the level of agreement with the diagnostic gold standard. Only 11 (16.2%) studies recommended a cutoff that prioritized the scale's sensitivity.

Discussion: It is important for clinicians to understand the difference between screening and diagnostic tests. Self-report questionnaires are intended as screening tools. The results of the present study indicate that most studies of the performance of the 3 most commonly studied bipolar disorder screening measures have taken the wrong approach in deriving the cutoff score on the scale for the purpose of screening.

Learning Objectives:

- Become familiar with the principles of screening and how this should inform the derivation of cutoff scores on self-report screening scales.
- Become aware of how scale developers and researchers have usually taken the wrong approach in deriving cutoff scores on screening measures for bipolar disorder.

Literature References:

- Griner P, Glaser R. Misuse of laboratory tests and diagnostic procedures. *N Engl J Med.* 1966;307:1336-1339.
- Hirschfeld R, Williams J, Spitzer R, et al. Development and validation of a screening instrument for bipolar spectrum disorder: The Mood Disorder Questionnaire. *Am J Psychiatry.* 2000;157:1873-1875.

MEASURING THE RELATIONSHIP BETWEEN PATIENT ADHERENCE TO ATYPICAL ANTIPSYCHOTICS AND THEIR OTHER MEDICATIONS*

Alison Silverstein, Precision Health Economics

Felicia Forma, Jason Shafrin, Darius Lakdawalla, Joanna MacEwan, Alison Silverstein, Ainslie Hatch

Abstract: Background: Patients with serious mental illness (SMI) often use multiple medications to treat their mental and physical illnesses. Innovations such as digital medicine technologies offer improved ability to track adherence in real time and provide this information to clinicians, but the utility of technological advances in adherence measurement depends on the number of medications that can be tracked by the technological platform and/or by how well adherence information to one tracked medication can predict patients' adherence to other medications that might not be tracked.

Objective: To examine how well patient adherence to atypical antipsychotic therapies predicts adherence to other medications to treat other SMIs, type 2 diabetes, or hypertension.

Methods: We measured adherence using claims data for patients with a diagnosis of schizophrenia, bipolar disorder, or major depressive disorder in the previous year. Patients were required to have both a prescription for an oral atypical antipsychotic as well as a prescription for another SMI therapy or an oral anti-diabetic or an antihypertensive in the same year. We measured concurrent adherence to both a patient's antipsychotic and one of 23 other medications using the proportion of days covered (PDC) over a 1 year time frame. Patients were considered adherent if $PDC \geq 0.80$. We calculated the accuracy, positive predictive value (PPV), and negative predictive value (NPV) of antipsychotic adherence in predicting adherence to their other concurrently taken medication.

Results: Among the 129,614 patients in our sample, the average age was 44.8 years (SD=14.8) and 13.0% were female. Median prediction accuracy based on atypical

antipsychotic adherence to the other 23 medications was 67% (range: 55% to 71%; statistically different from 50% accuracy in all cases, $p < 0.001$). Accuracy was also higher than estimates of physician predictions of adherence (accuracy=53%) from previous studies. The antipsychotic adherence's NPV of 75% (range: 62% to 88%) was generally higher than its PPV of 62% (range: 43% to 67%) and respectively, (all $p < 0.001$).

Conclusions: Information on antipsychotic adherence provides significant predictive power of patient adherence to other medications, indicating that technologies measuring adherence to antipsychotics may be useful for predicting adherence to other medications commonly used by patients with SMI. As NPV is higher than PPV, adherence to an antipsychotic is likely a necessary but not sufficient condition for patients with SMI to be adherent to their other medication.

Learning Objectives:

- To examine how well patient adherence to atypical antipsychotic therapies predicts adherence to other medications used to treat other severe mental illnesses, type 2 diabetes, or hypertension.
- To compare previously reported physician predictions of adherence with prediction accuracy based on atypical antipsychotic adherence.

Literature References:

- MacEwan JP, Forma FM, Shafrin J, Hatch A, Lakdawalla DN, Lindenmayer JP: Patterns of Adherence to oral atypical antipsychotics among patients diagnosed with schizophrenia. *J Manag Care Spec Pharm.* 2016; 22(11):1349-1361.
- Gorczynski P, Patel H, Ganguli R. Adherence to diabetes medication in individuals with schizophrenia: A systematic review of rates and determinants of adherence. *Clin Schizophr Relat Psychoses.* 2017; 10(4):191-200.

Wednesday, May 31, 2017

8:30 a.m. – 10:00 a.m.

Regulatory Plenary Session

REGULATORY PLENARY

Tiffany Farchione, US Food and Drug Administration, Islam Younis, US Food and Drug Administration; Valentina Mantua, Italian Medicines Agency; Luca Pani, European Medicines Agency

Overall Abstract: This year's plenary session will provide updates on major ongoing projects at FDA and EMA. FDA will present two initiatives. First is a Critical Path Initiative project entitled, "Optimizing Design Elements of Schizophrenia Clinical Trials." The goals of this project were to assess the feasibility of reducing the number of PANSS items, using time to dropout as a trial endpoint, and shortening trial duration. Topline data from the project will be shared during the plenary. FDA will also discuss our progress toward revising the Agency guidance on assessment of suicidal ideation and behavior in clinical trials. EMA will provide a general overview of current activities, including the PRIME (PRiority MEDicines) scheme and planned updates to guidelines.

**of special interest to clinicians*

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

ASCP Awards Ceremony and ASCP Lifetime Awardee Talk - David Kupfer: After Fifty Years, All Roads Converge

AFTER FIFTY YEARS, ALL ROADS CONVERGE

David Kupfer, University of Pittsburgh School of Medicine/Western Psychiatric Institute and Clinic

Overall Abstract: The last 50 years in clinical psychopharmacology have reflected both the major advances in neuroscience and the major frustrations in the clinical application of psychopharmacologic agents. My own voyage has been highlighted by many of the themes illustrative both of these advances and these frustrations. In this presentation, I shall briefly review the evolution of the concept of major depression as an example of diagnostic issues that have characterized this half-century and the accompanying views of prognosis. The use of clinical trials, primarily RCT's, has led to more precise terminology and methodological advances. The dialectic between dimensional and categorical approaches to diagnosis illustrates other important aspects of this period in psychopharmacology, as does the necessity of identifying biomarkers to track disease, to move in the direction of more precise prognoses and, ultimately, to elucidate underlying etiology.

Learning Objectives:

- Describe the evolution of the concept of MDD within the DSM framework.
- Describe advances in clinical trial methodology and accompanying analytic methods.

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

Wednesday Afternoon Panel Sessions

IMPACT OF ABNORMAL INVOLUNTARY MOVEMENTS ACROSS DIVERSE CLINICAL POPULATIONS*

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Overall Abstract: Abnormal involuntary movements have been recognized as core components of both mood and psychotic disorders since before the modern pharmacotherapy era. The introduction of first generation antipsychotics drew greater attention to treatment-emergent susceptibility to extrapyramidal side effects (EPS) as well as tardive dyskinesia (TD). Risks for these complications has been partly, but not fully, mitigated by the advent of second generation antipsychotics. The eventual development of TD correlates with age, antipsychotic dosage and exposure duration, positive symptoms of psychosis, and poor response to treatment in a first episode. Evidence for purported ethnic/racial differences in antipsychotic-related dystonic reactions and other adverse motor effects often fails to account for confounding factors such as antipsychotic dosing and exposure among clinical subgroups. Adverse motor effects in general often lead to diminished treatment adherence, poorer quality of life, and a more severe and refractory overall course of psychotic or affective illness. Phenomena involving abnormal movements can mimic signs of psychopathology (e.g., akathisia versus agitation or hypomania; akinesia versus depression or negative symptoms), underscoring the need for careful clinical assessment. Pharmacogenetic, family-history,

**of special interest to clinicians*

functional neuroimaging (notably, white matter changes) and other investigative approaches have begun to shed light on factors that may either predispose to, or result from, treatment-associated abnormal involuntary movements. Pharmacological strategies to counteract EPS have historically have been limited to dosage reductions, beta blockers, benzodiazepines, and anticholinergics; management strategies for TD have been notoriously meager.

This panel will provide an overview of epidemiologic, clinical, psychosocial and neurobiological correlates of EPS and TD and their association with affective, cognitive, positive and negative symptoms in schizophrenia, bipolar disorder and major depression. Particular attention will focus on clinical presentations and management of abnormal involuntary movements across diverse populations including racial subgroups, sex differences, older adults, children/adolescents, and first episodes. Differential risks for EPS and TD across individual agents will be described, alongside patient-specific clinical and neurobiological (e.g., pharmacogenetic) factors that may increase propensity for abnormal motor movements. Strategies to address adherence in the face of adverse motor effects will be reviewed in the context of an individual's understanding of risks and benefits of therapeutic modalities, competing or additional side effect concerns, and clear communication regarding side effect assessment and relative burden. Evidence for current and emerging pharmacological strategies to manage TD will be reviewed, including novel inhibitors of vesicular monoamine transporter 2 (VMAT2) and deuterated tetrabenazine, among other treatment approaches.

Learning Objectives:

- To recognize risk factors for extrapyramidal side effects (EPS) and tardive dyskinesia (TD) across specific antipsychotics and other psychotropic agents as well as clinical, pharmacogenetic and other neurobiological patient-specific vulnerabilities.
- To describe current and emerging psychosocial and pharmacological management strategies for EPS and TD.

PREVALENCE OF AKATHISIA, EPS AND TD ACROSS AGENTS AND PATIENT POPULATIONS*

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Incident rates of involuntary movement disorders vary across psychotropic agents as well as across populations of mood and psychotic disorder patients. While risks for akathisia, extrapyramidal side effects (EPS) and tardive dyskinesia (TD) appear lower with second- than first-generation antipsychotics, none appear risk-free. Associations between EPS and lithium or tricyclic antidepressants, as well as mirtazapine, duloxetine, and some serotonin reuptake inhibitors, are limited to case reports. A 2013 meta-analysis of schizophrenia clinical trials identified only clozapine as having a lower incidence of EPS than placebo while haloperidol, chlorpromazine, lurasidone, risperidone and paliperidone carried significantly greater EPS risks than placebo. Among second generation antipsychotics (SGAs), iloperidone and quetiapine appear least likely to cause akathisia across indications. Clinical trials with SGAs in bipolar disorder report incident rates of akathisia as much as 3-fold higher than in schizophrenia trials. First generation antipsychotics (FGAs) generally carry a 3-5%/year risk for causing TD. Randomized maintenance trials with SGAs have reported one-year incident rates of TD ranging from 0.52% (olanzapine) to as high as 13.4% (moderate-to-high-dose risperidone) with a weighted mean rate across SGAs of 0.8% in adults. and 5.3% in adults over age 54. Individuals with

bipolar disorder may be even more susceptible to EPS than adults with schizophrenia, with randomized trials revealing single-digit numbers needed to harm (NNHs) with risperidone or ziprasidone and double- or triple-digit NNH's with olanzapine or quetiapine, respectively; furthermore, during SGA treatment, bipolar depressed patients may be more prone to EPS than bipolar manic patients. Akathisia, unlike TD, appears to be a robustly dose-related phenomenon across first- and second generation antipsychotics.

A family history of primary movement disorders increases risk for EPS in FGA or SGA recipients. Prevailing theories about the pathogenesis of EPS and TD include not only dopamine supersensitivity and fast dissociation of drug ligands from striatal D2 dopamine receptors but, additionally, implication of allelic variants of candidate genes including the regulator of G-protein signaling gene (RGS9), the 5HT2Cser gene (5HTCR), the 5HT2A gene, the dopamine D3 ser9gly genotype (DRD3gly), the dopamine D4 gene (DRD4), the cannabinoid receptor type 1 gene (CB1), the melatonin 1A receptor gene (MTNR1A), the heparan sulfate proteoglycan of basement membrane gene (HSPG2), dipeptidyl peptidase like 6 gene (DPP6), the phosphatidylinositol-5-phosphate 4-kinase type 2 alpha gene (PIP5K2A), the vesicular monoamine transporter gene (SLC18A2), and interactions between 5HTCR and DRD3gly as well as the BDNF and DRD3 genes. Given the increasing use of SGAs for primary mood disorders, delineating genetic and other risk factors for adverse motor effects may hold particular importance in this population.

Learning Objectives:

- To describe and compare incident rates of akathisia, EPS, and TD across clinical trials of antipsychotic drugs and other psychotropic agents.
- To discuss pharmacodynamic and pharmacogenetic factors that may contribute to the development of abnormal motor movements in psychotic and mood disorder patients.

Literature References:

- Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 2004; 161: 414-425.
- Gao K, Kemp DE, Ganocy SJ, et al. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *J Clin Psychopharmacol* 2008; 28: 203-209.

WHO'S AT RISK FOR DRUG-INDUCED MOVEMENT DISORDERS? A FOCUS ON DIVERSITY OF PATIENT RISK FACTORS AND CLINICAL PRESENTATIONS*

Peter Weiden, Alkermes, Inc.

Individual Abstract: Background: The initiation, control, and coordination of volitional movements are a central part of normal CNS cortical function. The motor control systems are often closely linked to key emotional and cognitive neuronal tracks. It is not surprising that therapeutic receptor targets for psychiatric drugs can alter CNS motor system functioning. Problem: Many psychiatric medications can, and do, cause drug-induced movement disorders. All of the subtypes – EPS, akathisia and persistent dyskinesia – can cause considerable distress as well as safety concerns. The clinical presentations are often complex, subtle, and may overlap with some of the primary manifestations of the psychiatric condition. Further, the clinical presentation may be primarily a motor or movement problem, or a subjective or behavioral problem.

Discussion: Accurate identification requires a level of skill and understanding about the range of risk factors and complexity of clinical presentations. However, professional training in movement disorders is no longer integral to many psychiatrists because of the mistaken belief that newer antipsychotics are unlikely to cause movement disorders, as well as a secular shift in emphasizing metabolic risks of antipsychotics. Both of these factors have resulted in the unfortunate unintended consequence of neglected interest and training, with the consequence that all of the major variations of EPS, akathisia and persistent dyskinesia are missed, misdiagnosed, or misclassified.

Importance: Timely and accurate clinical recognition and correct attribution is as important now as it was when movement disorders were initially described over 50 years ago.

Learning Objectives:

- Help clinicians and investigators understand patient-level and disease-level risk factors for medication-induced movement disorders.
- Review some of the root causes for diagnostic under-recognition and mis-attribution of major movement disorder syndromes, including akathisia, antipsychotic-induced parkinsonism, and dyskinetic syndromes.

Literature References:

- Weiden, P. J., et al. (1987). "Clinical nonrecognition of neuroleptic-induced movement disorders: a cautionary study." *The American journal of psychiatry* 144(9): 1148-1153.
- Weiden, P. J. (2008). "Antipsychotic-induced movement disorders - forgotten but not gone." *Acta Psychiatrica Scandinavica* 117(6): 401-402.

TREATMENT ADHERENCE AND ANTIPSYCHOTIC-RELATED ADVERSE EFFECTS*

Martha Sajatovic, University Hospitals Case Medical Center

Individual Abstract: Antipsychotic drugs are associated with a variety of adverse effects that impact patient subjective response to treatment and ultimately treatment adherence. Subjective reports of “dysphoric” responses to first-generation antipsychotic drugs predicted medication adherence and formed the basis for early standardized adherence assessments used in patients with psychotic and mood disorders. Subsequent work noted that poor adherence is pervasive across among individuals with chronic psychotic and chronic mood disorders and driven by patient, medication, treatment and systems-related factors. A treatment registry study from the U.S. veteran’s health administration that included over 70,000 adults with bipolar disorder treated with antipsychotic drugs found adherence rates for atypical antipsychotics (except clozapine) to be fairly similar, ranging from 0.75 for risperidone to 0.79 for aripiprazole (0 to 1.0 medication possession ratio, 1.0 = perfect adherence). Mean adherence for individuals on two antipsychotics was somewhat higher than for single antipsychotics ($p < 0.0001$). For individuals who were on only one antipsychotic medication ($n = 21,917$), mean adherence for first-generation agents (0.82 ± 0.33) was higher than adherence for second-generation antipsychotic agents (0.75 ± 0.37) ($p < 0.0001$). These findings may reflect the fact that individuals who initially tolerate and derive symptomatic benefit are likely to sustain longer-term adherence.

Both experienced side effects and well as fear of side effects can lead to poor adherence. A recent literature review on the role of adverse effects impacting bipolar medication adherence found weight gain, perceived cognitive impairment, tremors, and sedation as the adverse

effects most likely to lead to non-adherence. Antipsychotic drugs may also be perceived as stigmatizing for some patients, especially in the case of first-generation compounds. Patient preference to avoid abnormal involuntary movements should be addressed in the context of an individual's understanding of risks and benefits of therapeutic options, competing or additional side effect concerns, and clear communication regarding side effect assessment and relative burden. Standardized instruments that assess and quantify the extent of side effects, perceived personal burden for a given side effect, and perceived concerns or risk may help guide shared decision-making that can support optimal adherence.

Learning Objectives:

- Participants will gain familiarity with effects of antipsychotic medications on treatment adherence in patients with chronic psychotic and with chronic serious mood disorders.
- Participants will learn about systematic assessments that may help identify and characterize relative burden of side effects from a patient perspective.

Literature References:

- Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, Docherty JP. Assessment of Adherence Problems in Patients with Serious and Persistent Mental Illness: Recommendations from the Expert Consensus Guidelines. *Journal of Psychiatric Practice*, 16(1): 34-45, 2010.
- Mago R, Borra D, Mahajan R. Role of adverse effects in medication non-adherence in bipolar disorder. *Harv Rev Psychiatry*. Nov-Dec;22(6):363-6. 2014

CURRENT AND EMERGING TREATMENTS FOR DRUG INDUCED MOVEMENT DISORDERS*

Andrew Cutler, Meridien Research

Individual Abstract: Dopamine receptor blockers, such as antipsychotic drugs can cause a variety of drug induced movement disorders (DIMD). Acute dystonia, EPS and akathisia usually appear early in treatment or soon after dose increase. They are treated with anticholinergic medication, benzodiazepines or beta blockers. Other movement disorders can emerge later and include the tardive syndromes. Tardive dyskinesia (TD), which is characterized by involuntary choreoathetoid movements in any part of the body, but especially the orobuccal and lingual regions of the face, is especially challenging and usually persists after discontinuation of the offending agent. While newer atypical antipsychotics (AAPs) appear to have somewhat lower risk for inducing DIMD, the risk is still significant, and AAPs are being increasingly used for a broader range of indications and in younger patients. This widespread use of antipsychotics means that the incidence of DIMDs, especially TD may actually be increasing. Many treatments have been studied, but effective treatment has remained elusive. Anticholinergics in particular are ineffective and may actually worsen TD. Recently 2 new medications in late stage development have shown promise for the treatment of TD, and if approved, could be available in 2017. They are both modifications of tetrabenazine, a VMAT2 inhibitor, and presumably work by moderating a dysregulated dopamine system via making less dopamine available to this oversensitive system.

Deutetabenazine is deuterated tetrabenazine. Deuteration theoretically makes chemical bonds stronger, thus slowing metabolism of the compound, and favorably altering its pharmacokinetic properties by delaying Tmax, lowering Cmax and decreasing peak-to-trough

variability. This results in less frequent dosing (BID vs TID or QID for tetrabenazine), and a better tolerability profile. Studies for Huntington's Chorea were positive, and it should be approved for this indication in early 2017. Positive results from a Phase III trial for TD were presented earlier this year, and recently results from a second positive trial have been announced. It is anticipated that deutetrabenazine could be approved later in 2017.

Valbenazine was created by choosing one of the four isomers of tetrabenazine and modifying it by adding valine. The isomer used is the "cleanest" in the sense that it is the most selective for VMAT2, whereas the others have affinity for various receptors, including dopamine.

This creates a new chemical entity which only requires QD dosing, and has a very favorable safety and tolerability profile. Two positive Phase III trials for TD have been reported and submitted to the FDA for review.

After over 60 years of virtually no effective treatments for TD, it would be a major breakthrough for either or both of these new medications to become available to clinicians to finally be able to treat this devastating condition.

Learning Objectives:

- Participants will be able to distinguish between various Drug Induced Movement Disorders and recognize that tardive dyskinesia is a special clinical challenge with no currently approved treatments.
- Participants will become familiar with deutetrabenazine and valbenazine, which have both shown efficacy in Phase III trials and could soon be FDA approved to treat TD.

Literature References:

- Caroff SN, et al. Movement Disorders Induced by Antipsychotic Drugs: Implications of the CATIE Schizophrenia Trial. *Neurol Clin*, 29(1):127-148.
- Waln O, Jankovic J. An Update on Tardive Dyskinesia: From Phenomenology to Treatment. Louis ED, ed. *Tremor and Other Hyperkinetic Movements*. 2013;3:tre-03-161-4138-1.

OPTIMIZING NEUROMODULATORY AND PHARMACOLOGIC APPROACHES TO TREATMENT REFRACTORY DEPRESSION*

Michael Henry, Massachusetts General Hospital

Overall Abstract: Treatment refractory depression is a common clinical problem with significant morbidity. Although algorithms have been proposed for defining the clinical syndrome, the definition in clinical practice often reflects a mix of clinical acuity and past treatment failures. As a result, the optimal treatment approach is not clear. This panel will discuss the available data for choosing and optimizing the pharmacologic, TMS and ECT approaches to treating treatment refractory depression in the clinical setting.

Recent advances in the pharmacologic approaches to treatment refractory depression, including ketamine will be discussed with an emphasis on practical clinical applications.

Advances in TMS technique, including a consideration of the role of magnet placement, stimulus, dosing, and concomitant medications will be presented.

The presentation on ECT will include a discussion of the interaction of concomitant medications, anesthetic choices, electrode placement, and stimulus dosing.

Learning Objectives:

- Participants will understand the key features behind the clinical designation of treatment refractory depression.

- Participants will learn strategies for optimizing pharmacologic and neuro-modulatory treatments for depression.

PHARMACOLOGICAL STRATEGIES IN THE TREATMENT OF RESISTANT DEPRESSION

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: In major depressive disorder (MDD), a substantial proportion of depressed patients show only partial or no response to standard antidepressant therapies, and, even among responders to antidepressant treatment, residual symptoms are rather common. When patients with MDD do not respond adequately to treatment with an antidepressant, clinicians may choose a pharmacology strategy aimed at treating this form of resistant depression. The typical pharmacological strategies are 1) the use of high doses of antidepressants, 2) switching to a different antidepressant, 3) using a pharmacologic agent that is not considered to be a standard antidepressant to boost or enhance the effect of an antidepressant that is continued (augmentation), and 4) combining the antidepressant that did not produce adequate response with another antidepressant, typically of a different class (combination). With respect to the augmentation and combination strategies, there are a number of placebo-controlled clinical among patients with treatment-resistant depression, showing the efficacy of various pharmacological tactics. The best studied augmentation strategies involve the use of atypical antipsychotic agents, ketamine and other glutamergic compounds, dopaminergic agents, anti-inflammatory psychotropic drugs, and opioid modulators. The best studied combination strategies involve the use of SSRIs or SNRIs with bupropion or mirtazapine. On the other hand, clinicians' decisions are often guided also by anecdotal reports, case series, and by some relatively smaller, uncontrolled clinical trials. All these augmentation and combination strategies appear to be relatively safe and effective approaches to treatment-resistant depressions. While drug-drug interactions may limit the use of some of these strategies, the potential loss of partial benefit from the failed drug inherent in switching may increase the acceptability of augmentation and combination strategies among partial responders. This presentation will review the evidence for efficacy of these pharmacological strategies in the treatment of resistant depression.

Learning Objectives:

- Participants will learn about the typical pharmacological strategies used in the treatment of resistant depression.
- They will also become familiar with the evidence of efficacy of these various strategies.

Literature References:

- Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, Ritz L, Nierenberg AA, Lebowitz BD, Biggs MM, Luther JF, Shores-Wilson K, Rush AJ; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med.* 2006 Mar 23;354(12):1243-52.
- Fava M, Rush AJ. Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. *Psychother Psychosom.* 2006;75(3):139-53.

OPTIMIZING TRANSCRANIAL MAGNETIC STIMULATION (TMS) THERAPY FOR TRD*

Tracy Barbour, Harvard Medical School/Massachusetts General Hospital

Individual Abstract: Transcranial Magnetic Stimulation is a noninvasive neuromodulation technology with FDA clearance for the treatment major depressive disorder. Effectiveness naturalistic studies have reported a 41.5-58% response and 26.5-37.1% remission rate. Despite its positive impact on TRD patients, a number of them continue not to respond, highlighting the need to develop additional strategies that increase the therapeutic benefit. In this talk we will discuss a framework to consider optimization of TMS in TRD and discuss the basic and clinical evidence, even if in its early stages. We will discuss the concept of TMS dose, the impact of individualized neuroimaging-guided stimulation, the role of laterality, novel stimulation protocols (including new targets and sequences), the role of TMS coils and augmentation of TMS with behavioral or pharmacological interventions.

Learning Objectives:

- To understand a framework to consider optimization of TMS antidepressant benefits.
- To understand specific strategies and their evidence.

Literature References:

- Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. *Depression and anxiety*. 2012;29(7):587-96.
- Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. *J Clin Psychiatry*. 2014;75(12):1394-401.

STRATEGIES FOR OPTIMIZING ECT: INTEGRATION OF PHARMACOLOGY, ANESTHESIA AND STIMULUS PARAMETERS*

Michael Henry, Massachusetts General Hospital

Individual Abstract: Electroconvulsive therapy (ECT) has evolved from a technique focused on the induction of a seizure to one focused on the optimization of the seizure induced. Brain imaging studies indicate that electrode placement and stimulus intensity combine with the individual's physiology to determine the amount of brain tissue impacted by each treatment. Accordingly, Sackeim and colleagues demonstrated that stimulus intensity relative to the individual's seizure threshold is a clinically important variable for efficacious unilateral treatment. Several factors influence the brain's seizure threshold and have significant impact on the treatment parameters need to produce a clinical significant antidepressant effect.

Two of the more important variables that can be controlled in clinical practice are the concomitant medications the patient takes during the course of treatment and the choice of anesthetic agent. The effects of various classes of psychopharmacologic agents on seizure threshold can be unclear. The available evidence on the effects antidepressants, benzodiazepines, and anticonvulsants on seizure threshold and treatment efficacy will be reviewed. Similarly, anesthetic agents work directly on the central nervous system and depending on dose and mechanism can have vastly different effects on seizure threshold.

Methohexital, for example, when used in neurosurgery at low doses can induce seizures. When used in higher doses for ECT anesthesia it raises seizure threshold. Using meta-analytic techniques, this talk will describe the effects of anesthetics commonly used for ECT on seizure threshold and treatment efficacy. Particular emphasis will be placed on studies that have used ketamine to augment the antidepressant effects of ECT.

The effective integration of electrode placement, concomitant pharmacology, and anesthesia contributes to optimization of clinical outcome and reduction of adverse effects from ECT.

Learning Objectives:

- Participants will appreciate the interaction between ECT treatment parameters, electrode placement, and concomitant medications.
- Participants will understand the impact of choice of anesthetic agent on treatment efficacy.

Literature References:

- Sackeim HA, Decina P, Portnoy S, Neeley P, Malitz S. Studies of dosage, seizure threshold, and seizure duration in ECT. *Biol Psychiatry* 1987; 22_249-68.
- Henry ME, Schmidt ME, Moatochik JA, Stoddard EP, Potter WZ. Effects of ECT on Brain Glucose: A pilot FDG PET study.

REGULATORY AND METHODOLOGICAL CONSIDERATIONS IN THE EVALUATION OF DRUG DEPENDENCE IN THE CLINICAL SETTING

Beatrice Setnik, INC Research

Overall Abstract: Evaluating drug withdrawal effects is an integral component of dependence potential, which informs the overall safety, appropriate dosing, and scheduling of a drug. Understanding withdrawal phenomenon is critical in the care and management of patients who are physically dependent on medication or drugs of abuse. The methodological approaches to assess dependence continue to evolve and require careful evaluation of both preclinical and clinical data. Physical dependence can manifest from various drug classes including classes of drugs that are and are not associated with substance use disorder (e.g. beta blockers, corticosteroids). Preliminary approaches often include animal models to evaluate behavioral and physical manifestation of withdrawal, however translation to humans can be challenging. In the clinical setting, evaluation of withdrawal requires characterization of a drug's pharmacology to determine what type of symptoms may manifest upon abrupt discontinuation. Furthermore, rebound phenomenon resulting in a worsening of symptoms of the treated disease as a result of abrupt discontinuation, is also an important study assessment (Fontaine et al 1984). Study populations must be carefully considered, particularly in patient populations that cannot be safely withdrawn from study drug. Clinical trials must determine what population, duration of maintenance and endpoints are relevant for a given drug. For example, the time to establish dependence to a benzodiazepine can vary by drug type and dose and can range from 4 to 12 weeks (Mackinnon and Parker, 1982). Commonly adverse events and drug-specific withdrawal scales are included to evaluate withdrawal symptoms, however other pharmacodynamics measures may also be considered. The administration of endpoints and safety monitoring requires also practical considerations in the context of larger patient trials, where confined stays may not be possible following abrupt discontinuation. This workshop will address the regulatory and methodological considerations that are rapidly evolving in this active area of research and will cover case examples of studies examining drug withdrawal and dependence. In addition, the clinical relevance of dependency and mitigation of symptoms in the clinical setting will be discussed.

Learning Objectives:

- Learn about the regulations and requirements surrounding the evaluation of physical dependency of CNS active drugs.
- Understand the clinical methods and outcome measures needed to evaluate physical dependency in the clinical setting.

REGULATORY CONSIDERATIONS IN THE ASSESSMENT OF DRUG DEPENDENCE AND WITHDRAWAL IN HUMANS.

Jack Henningfield, Pinney Associates

Individual Abstract: Abuse and dependence/withdrawal, and overdose associated with the use of illicitly manufactured and prescription drugs including opioid pain relievers, benzodiazepines, cocaine and heroin are serious public health problems. Various federal agencies, including the National Institute on Drug Abuse, Substance Abuse and Mental Health Services Administration, Centers for Disease Control and Prevention, and the Food and Drug Administration (FDA) are coordinating efforts to provide the science foundation for understanding the problems and to more effectively prevent and treatment them. The major focus of the FDA is to encourage and support the development of less abusable and safer new medications, the development of abuse deterrent formulations for existing medicines, and to ensure accurate labeling of the risks and benefits of approved products with respect to their potential for abuse and dependence. The FDA's recommendations concerning drug approval and labeling (including Controlled Substances Act (CSA) recommendations pertaining to potential drug scheduling) must be informed by nonclinical and clinical research, and other relevant science. Among the most important data for CSA recommendations and related labeling are the results of clinical abuse potential studies, and safety and efficacy clinical trials. Critical to this is the use of study designs and measures that will provide the FDA with reliable and valid information to guide its recommendations and actions. Such data are integrated into the FDA's 21st Century drug review process. Such clinical study evaluations of drug abuse, and dependence and withdrawal related effects are also necessary: 1) to inform physicians and patients whether or not the drug can be abruptly withdrawn at the end of treatment; 2) to inform physicians and patients of dangers and consequences of abrupt withdrawal symptoms; 3) to inform subjects abusing the drug about health consequences of the development of dependence and consequences of drug withdrawal. During FDA review of the New Drug Application (NDA), the drug's dependence potential is evaluated taking all nonclinical and clinical findings into account. The Agency's regulatory actions regarding its evaluation include product labeling warnings to ensure safe use and prescribing and/or scheduling evaluations under the Controlled Substances Act (CSA). This presentation will provide an overview of the methods and approaches for designing clinical studies and interpreting the findings to enable the FDA to develop recommendations and actions that are based on a strong science foundation are will be likely to serve to improve the practice of medicine and public health of the United states.

Learning Objectives:

- Attendees will learn about the current state of the art methods for assessing abuse and dependence/withdrawal in clinical studies.
- Attendees will learn how the FDA uses such data to develop its recommendations concerning Controlled Substances Act scheduling recommendations and labeling including abuse and dependence related risks and management, as well as potential abuse deterrent related claims.

Literature References:

- Food and Drug Administration (FDA): Guidance for industry: Assessment of abuse potential of drugs, draft guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Silver Spring, MD, 2010
- Food and Drug Administration (FDA): Abuse-deterrent opioids - Evaluation and labeling, guidance for industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Silver Spring, MD, 2010

CLINICAL METHODS TO EVALUATE PHYSICAL DEPENDENCY AND WITHDRAWAL FOLLOWING ABRUPT DRUG DISCONTINUATION

Beatrice Setnik, INC Research

Individual Abstract: Evaluating drug withdrawal effects is an integral component of dependence potential, which informs the overall safety and appropriate dosing. Regulatory agencies, such as the FDA, require evaluation of dependency to inform scheduling decisions for newly approved drugs. The methodological approaches to assess physical dependence (withdrawal symptoms) in the clinic continue to evolve. In the clinical setting, evaluation of withdrawal requires characterization of a drug's pharmacology to determine what type of symptoms may manifest upon abrupt discontinuation. Furthermore, rebound phenomenon resulting in a worsening of symptoms of the treated disease as a result of abrupt discontinuation, is also an important study assessment (Fontaine et al 1984). Study populations must be carefully considered, particularly in patient populations that cannot be safely withdrawn from study drug. Clinical trials must determine what population, duration of maintenance and endpoints are relevant for a given drug. For example, the time to establish dependence to a benzodiazepine can vary by drug type and dose and can range from 4 to 12 weeks (MacKinnon and Parker, 1982). Commonly adverse events and drug-specific withdrawal scales are included to evaluate withdrawal symptoms, however other pharmacodynamics measures may also be considered. The administration of endpoints and safety monitoring requires also practical considerations in the context of larger patient trials, where confined stays may not be possible following abrupt discontinuation. Methodological approaches including study design and appropriate patient populations will be discussed.

Learning Objectives:

- Review the methods to assess physical dependency (drug withdrawal) in clinical studies.
- Understand how to select the appropriate study population to evaluate withdrawal symptoms.

Literature References:

- Fontaine R, Chouinard G, Annable, L, Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. *Am J Psychiatry*. 1984 Jul;141(7):848-52.
- MacKinnon GL, Parker WA. Benzodiazepine withdrawal syndrome: a literature review and evaluation. *Am J Drug Alcohol Abuse*. 1982. 9(1):19-33.

PRACTICAL CONSIDERATIONS REGARDING THE ADMINISTRATION OF PHARMACODYNAMIC MEASURES TO EVALUATE PHYSICAL DEPENDENCY AND WITHDRAWAL FOLLOWING ABRUPT DRUG DISCONTINUATION

Denise Milovan, INC Research

Individual Abstract: The clinical assessment of tolerance/dependence and withdrawal associated with an investigation drug is governed by FDA, EMA, and ICH regulations. The pre-clinical evaluation of dependence and withdrawal provides meaningful insights and can point to a prospective concern for human dependence; however, the assessment of human dependence can prove more complex than indicated by data obtained from animal studies and require careful determination of potential for abuse, dependence, and symptoms of withdrawal. The development of scientifically sound clinical studies to ascertain a drug's potential to produce physical dependence, clarify whether abrupt discontinuation may be associated with withdrawal symptoms and, if so, adequately characterize these symptoms, relies on the selection of suitable study populations, study design, and sensitive pharmacodynamic scales.

Upon discontinuation of a drug, physical dependence is associated with (1) recurring symptoms in patients treated for a disorder and (2) withdrawal effects which include signs and symptoms related to the disruption of neurotransmitter systems affected by the pharmacology and pharmacokinetics of the drug (American Psychiatric Association, 2013). Adequate characterization of the withdrawal- or discontinuation-emergent effects of a drug relies on the interpretation of results from multiple qualitative and quantitative data sources including adverse events related to abuse and dependence potential, physiological parameters, cognitive instruments, psychiatric scales, and outcomes from withdrawal instruments (Tiffany et al, 2011). In general, well-validated structured instruments or checklists should be selected for the evaluation of dependence and withdrawal.

Different classes of CNS drugs include both common withdrawal and new withdrawal symptoms (e.g., nausea, headaches, anxiety, sleep disturbances, tremor, irritability, agitation, decreased concentration, dysphoria, depression), but also have withdrawal symptoms specific to the drug class. The pharmacological class of the compound will generally inform the selection of specific scales. Most withdrawal scales have been developed on the basis of adverse effects experienced once a drug was discontinued (e.g., SSRI, opioid, benzodiazepine, cannabis withdrawal scales) and include both clinician-rated assessments and subject self-report questionnaires. Examples of drug class specific scales include: Discontinuation Emergent Signs and Symptoms Checklist, Subjective Opiate Withdrawal Scale, Penn Physician Withdrawal Checklist, Cannabis Withdrawal Scale. Mood-related scales (e.g., Beck Depression Inventory, Hospital Anxiety and Depression Scale, Spielberger State Anxiety Inventory, Columbia-Suicide Severity Rating Scale) are anticipated to be incorporated for all drug classes. Physiological parameters (e.g., heart rate, blood pressure, pupil diameter, and skin temperature) may be assessed if abrupt drug discontinuation is expected to elicit physiological autonomic responses of import. Similarly, cognitive instruments (e.g., Choice Reaction Time, Divided Attention Test, Hopkins Verbal Memory Test - Revised) may be included if dosing cessation may be associated with cognitive disturbances such as diminished attention or memory impairment.

This presentation will address some of the practical considerations regarding the selection of measures that will efficiently evaluate dependency and withdrawal.

Learning Objectives:

- Practical considerations when selecting pharmacodynamic measures to evaluate dependency and withdrawal.
- Balancing selection of measures against treatment compliance and study feasibility.

Literature References:

- Diagnostic and statistical manual of mental disorders. 1st ed. Washington, D.C.: American Psychiatric Association; 2013.
- Tiffany S, Friedman L, Greenfield S, Hasin D, Jackson R: Beyond drug use: a systematic consideration of other outcomes in evaluations of treatments for substance use disorders. *Addiction* 2011; 107:709-718

MEDICATION OR PSYCHOTHERAPY AS FIRST-LINE TREATMENT FOR POSTTRAUMATIC STRESS DISORDER? AN UPDATE ON THE CLINICAL PRACTICE GUIDELINES FOR THE PREVENTION AND TREATMENT OF PTSD*

Lori Davis, Veterans Affairs Medical Center

Overall Abstract: The Clinical Practice Guidelines for the treatment of Posttraumatic Stress Disorder (PTSD) have recently undergone extensive updating by a collaborative workgroup consisting of PTSD experts from the Veterans Administration and the Department of Defense, including two speakers on this panel. The panel will present the recent evidence from randomized controlled trials and systematic reviews that led to these important updates of the PTSD Clinical Practice Guidelines. In particular, the recommendation as to whether medication or psychotherapy should be offered as first-line treatment was a primary question that required extensive scrutiny and debate amongst the VA-DoD workgroup members. The panelists will discuss this important treatment dilemma, as well as, the interventions aimed at the prevention of PTSD and augmentation or alternative strategies in patients who fail to respond to first-line treatment.

Dr. Birur will begin the panel with a presentation of the evidence-based interventions delivered immediately post-trauma that serve to treat acute stress symptoms and prevent the development of PTSD. Trauma-focused cognitive behavioral therapy and modified prolonged exposure therapy delivered within weeks of a potentially traumatic event for people showing signs of distress have the most evidence in the treatment of early stress symptoms and the prevention of PTSD. Even though several pharmacological agents have been tried, only hydrocortisone prior to high-risk surgery, severe traumatic injury, or during acute sepsis has adequate evidence for effectiveness in the reduction of acute stress symptoms and prevention of PTSD. Next, Dr. Rauch will review the psychotherapy interventions and the evidence that supports trauma-focused cognitive behavioral therapy as first-line treatment for PTSD. She will explore the second-line psychotherapies in development that are most promising. In the third presentation, Dr. Davis will review the clinical treatment guidelines for the use for or against certain medications, including updates on antidepressants, prazosin, atypical antipsychotics, and augmentation strategies. She will discuss the rationale for and against offering trauma-focused psychotherapies over medication as first line treatment for PTSD. Dr. Norrholm will discuss translational research that interfaces with PTSD severity and treatment. Each panelist will conclude their talk with a gap analysis and a vision of future research in the prevention and treatment of PTSD. Dr. Shelton will serve as the panel's distinguished discussant and will highlight how translational research approaches may help illuminate the best PTSD treatment choices.

Learning Objectives:

- The participant will have an understanding of the most up-to-date Clinical Practice Guidelines for Posttraumatic Stress Disorder (PTSD).
- The participant will have an understanding of the evidence that supports the recommendation of trauma-focused psychotherapy as first-line for the treatment of PTSD.
- The participant will gain appreciation for translational research initiatives in the treatment of PTSD.

AN EVIDENCE BASED REVIEW OF EARLY INTERVENTION AND PREVENTION OF POSTTRAUMATIC STRESS DISORDER*

Badari Birur, University of Alabama, Birmingham

Individual Abstract: Background: An evidence-based review of post-trauma interventions used to prevent acute stress disorder (ASD) and posttraumatic stress disorder (PTSD) will be presented.

Methods: Literature search of PubMed from 1988 to March 2016 using keywords “Early Intervention AND Prevention of PTSD” yielded 142 articles, of which 52 intervention studies and 6 meta-analyses were included in our review.

Results: Trauma-focused cognitive behavioral therapy and modified prolonged exposure delivered within weeks of a potentially traumatic event for people showing signs of distress have the most evidence in the treatment of acute stress and early PTSD symptoms, and the prevention of PTSD. Even though several pharmacological agents have been tried, only hydrocortisone prior to high-risk surgery, severe traumatic injury, or during acute sepsis has adequate evidence for effectiveness in the reduction of acute stress symptoms and prevention of PTSD.

Conclusion: There is an urgent need to determine the best targets for interventions after trauma to accelerate recovery and prevent ASD and PTSD.

Learning Objectives:

- The participant will understand the various psychological and pharmacological interventions utilized in the prevention of acute stress disorder and posttraumatic stress disorder.
- The participant will be aware of the evidence-based treatments for prevention of acute stress disorder and posttraumatic stress disorder.

Literature References:

- Qi W, Gevonden M, Shalev A. Prevention of Post-Traumatic Stress Disorder After Trauma: Current Evidence and Future Directions. *Curr Psychiatry Rep.* 2016 Feb; 18(2):20. doi: 10.1007/s11920-015-0655-0. Review.
- Sijbrandij M, Kleiboer A, Bisson JJ, Barbui C, Cuijpers P. Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. *Lancet Psychiatry.* 2015 May; 2(5):413-21. doi: 10.1016/S2215-0366(14)00121-7.

AN EVIDENCE BASED REVIEW OF PSYCHOTHERAPY INTERVENTIONS FOR TREATMENT OF POSTTRAUMATIC STRESS DISORDER*

Sheila Rauch, Atlanta VAMC/Emory University School of Medicine

Individual Abstract: Background: Recent updates to treatment guidelines (NICE, IOM report, ISTSS, have summarized advances in the evidence base for the efficacy and effectiveness of psychotherapy for treatment of PTSD. We present a summary of these treatment guidelines for posttraumatic stress disorder (PTSD).

Methods: We will present current expert guidelines for the psychotherapeutic treatment of PTSD, including the NICE, ISTSS, IOM report, VA/DOD, APA, etc.

Results: Trauma-focused cognitive behavioral therapy is consistently supported as a first line treatment for PTSD. Guidelines vary in what a second line intervention may be as well as what psychotherapies in development are most promising. In addition, how to best implement these interventions in cases of partial or non-response are unclear. We will compare and contrast guidelines and present priorities for future research.

Conclusion: Several trauma focused psychotherapies have established effectiveness in the treatment of PTSD. Treatment for partial and non-responders to these first line treatments is unclear and guidelines vary in recommendations.

Learning Objectives:

- Attendees will learn what psychotherapeutic interventions are recommended for PTSD treatment across guidelines.
- Attendees will learn about psychotherapies in development.

Literature References:

- VA/DOD Clinical Practice Guideline 2010
- ISTSS Clinical Practice Guideline

CLINICAL PRACTICE GUIDELINES FOR THE PHARMACOTHERAPY OF POSTTRAUMATIC STRESS DISORDER*

Lori Davis, Veterans Affairs Medical Center

Individual Abstract: The Clinical Practice Guidelines for the treatment of Posttraumatic Stress Disorder (PTSD) have recently undergone extensive updating by a collaborative workgroup consisting of PTSD experts from the Veterans Administration and the Department of Defense. Dr. Davis will present the recent evidence from randomized controlled trials and systematic reviews that led to these important updates of the PTSD Clinical Practice Guidelines, specifically as it relates to pharmacotherapy. Dr. Davis will review the clinical treatment guidelines for the use for or against certain medications, including updates on antidepressants, prazosin, atypical antipsychotics, and augmentation strategies. She will discuss the rationale for and against offering trauma-focused psychotherapies over medication as first line treatment for PTSD. She will conclude her talk with a gap analysis and a vision of future research in the prevention and treatment of PTSD.

Learning Objectives:

- The participant will understand the hierarchy of pharmacotherapeutic treatments for PTSD, in terms of recommendations for or against certain medications.
- The participant will be aware of the evidence-based treatments for PTSD and gaps in the understanding of pharmacotherapy for PTSD.

Literature References:

- Cusack K, Jonas DE, Forneris CA, Wines C, Sonis J, Middleton JC, Feltner C, Brownley KA, Olmsted KR, Greenblatt A, Weil A, Gaynes BN. Psychological treatments for adults with posttraumatic stress disorder: A systematic review and

meta-analysis. *Clin Psychol Rev.* 2016 Feb;43:128-41. doi: 10.1016/j.cpr.2015.10.003. Epub 2015 Nov 2.

- Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. *Depress Anxiety.* 2016 Sep;33(9):792-806. doi: 10.1002/da.22511. Epub 2016 Apr 29.

TRANSLATING THE FACILITATION OR IMPAIRMENT OF FEAR ACQUISITION AND EXTINCTION MEMORIES IN TRAUMA-, STRESSOR-, AND ANXIETY-RELATED DISORDERS: IMPLICATIONS FOR PTSD TREATMENT*

Seth Norrholm, Emory University School of Medicine

Individual Abstract: Trauma-, stressor-, and anxiety-related disorders such as posttraumatic stress disorder (PTSD) represent a heterogeneous class of disorders that affects individuals exposed to trauma (e.g., combat, interpersonal violence) and chronic stress. PTSD, for example, is characterized by hyperarousal, intrusive reminders of the trauma, avoidance of trauma-related cues, and negative cognition and mood. Fear conditioning is a robust, translational experimental paradigm that can be employed to study the fear-related dimensions of PTSD (e.g., fear extinction, inhibition, and generalization). Our current program of studies highlights the versatility of fear conditioning paradigms, the implications for pharmacological and non-pharmacological treatments, the robustness of these paradigms to span an array of neuroscientific measures, and finally the need to understand the boundary conditions under which these paradigms are effective. Our work has shown that the expression of conditioned fear and the extinction of this type of learned fear (a learning and memory process that underlies exposure-based cognitive behavioral treatments) is significantly altered in both combat³ and civilian⁴ traumatized populations. In short, civilian populations have exhibited an over-expression of fear learning that we have termed fear load whereas combat veterans from Iraq and Afghanistan have showed an impaired ability to extinguish conditioned fear. Emerging evidence suggests that these fear extinction profiles are influenced by intrinsic (e.g., hormonal states) and extrinsic factors (e.g., rearing environment). Further understanding these paradigms will ultimately allow for optimization of fear conditioning and extinction learning paradigms, a necessary step towards the advancement of PTSD treatment methods.

Learning Objectives:

- To facilitate a broader understanding of translational psychiatry and its implications for treatment and relapse prevention.
- To discriminate between pharmacological and non-pharmacological means for enhancing exposure therapies.

Literature References:

- Norrholm SD, Jovanovic T, Olin IW, et al. (2010). Fear extinction in traumatized civilians with posttraumatic stress disorder: relation to symptom severity. *Biol Psychiatry*, 69(6), 556-563.
- Norrholm SD, Glover EM, Stevens JS, et al. (2014). Fear load: The psychophysiological over-expression of fear as an intermediate phenotype associated with trauma reactions. *Int J Psychophysiol*, 98(2 pt 2), 270-275.

2:30 p.m. – 3:30 p.m.

FDA 101 Session

CARE AND FEEDING OF AN INVESTIGATIONAL NEW DRUG (IND)

Keith Kiedrow, Hiren Patel, Kofi Ansah, William Bender, Kimberly Updegraff, US Food and Drug Administration

Overall Abstract: The Division of Psychiatry Products (DPP) is part of the Office of New Drugs (OND) in the Center for Drug Development and Research (CDER) at the Food and Drug Administration (FDA). The Division reviews matters related to Investigational New Drug (IND) Applications and New Drug Applications (NDAs) for indications ranging from Schizophrenia and Major Depressive Disorder to Autism and Insomnia. As an investigator, it is important to know and understand the definition of an IND as set forth under 21 CFR 312.3, as well as FDA's interpretation. In addition, investigators must be aware of the responsibilities related to IND submission and maintenance and must understand that these responsibilities differ depending on whether the investigator is participating as part of an industry-funded clinical trial or as an individual investigator. For the individual investigator, there are many things to consider such as whether an IND is necessary, what to include in an application, what happens after the application is submitted, and reporting requirements for on-going studies. The FDA has numerous resources available to help investigators navigate the process.

Learning Objectives:

- Briefly discuss the Division of Psychiatry Products' place and role in the FDA.
- Provide background information about Investigational New Drug (IND) applications, related regulations, and the IND's place in the timeline of new drug development.
- Discuss the roles and responsibilities of investigators in industry-funded clinical trials.
- Discuss the roles and responsibilities of individual investigators acting as sponsor-investigators.
- Provide a list of FDA sources that are available to Sponsors, Investigators, Researchers.

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

Wednesday Afternoon Workshops

HOT BUTTON TOPICS IN NEGOTIATION FOR MID-CAREER PROFESSIONALS IN PSYCHOPHARMACOLOGY AND ALLIED FIELDS*

Andrea Schneider, Marquette University Law School

Overall Abstract: This session will examine the tendencies that each person has when confronted with a conflict. We discuss the strengths and weaknesses of these common conflict styles and, most importantly, when to use these styles based on context and the other side. We then turn to the skills necessary to utilize each of these styles. Studies have shown that effective negotiators operate at high levels of assertiveness, empathy, and flexibility. Knowing how to build on each of these skills—and when and how to utilize them—are

**of special interest to clinicians*

crucial for effective negotiators. This session will use micro exercises and frameworks to help build each of these skill levels.

Learning Objectives:

- To understand your own defaults and tendencies when approaching conflict.
- To build on your own skill set, understanding how to utilize your strengths and where there is opportunity and necessity for growth.

NOVEL APPLICATIONS OF KETAMINE*

Waguih IsHak, Cedars-Sinai Medical Center and UCLA

Overall Abstract: Ketamine, it is best known as an illicit, psychedelic club drug. Often referred to as “special K” by the media, it was synthesized in 1962 and was approved in 1970 as an anesthetic for human use. During the Vietnam War, it was used as an anesthetic to relieve pain in wounded soldiers. Ketamine has been used in subanesthetic doses as a treatment for chronic pain and more recently for treatment of depression. Studies have shown that it can reverse within 45 minutes to hours- the kind of severe, suicidal depression that traditional antidepressants can’t treat and would take months to accomplish. This workshop will address novel application of ketamine in co-morbid chronic pain and depression, and using it to treat depression in the context of Parkinson's disease. Interestingly, ketamine’s effects on depression showing that it can reverse within 45 minutes to hours- the kind of severe, suicidal depression that traditional antidepressants can’t treat and would take months to accomplish. The effects last at least 5 days, far outlasting than its concentration in blood or tissue. An understanding of ketamine’s mechanism of action, which could lead to improved treatment, has been widely sought. In the most recent study in Nature May 2016, researchers provide evidence to indicate that it is not ketamine itself, but one of its metabolites, that is responsible for the drug’s antidepressant effects. The drawback of ketamine is that its effects are short-lived and its relief is temporary. Clinical trials at National Institute of Mental Health (NIMH) have found that relapse usually occurs about a week after a single infusion. To be used as an effective antidepressant, it would need to be administered IV regularly. The guidelines, which follow the protocol used in the NIMH call for six IV drips over a two-week period. The dosage is very low, about a tenth of the amount used in anesthesia. To be most effective for pain management, current data suggested prolonged infusion (4-14 days) for analgesic effects up to 3 months. Ketamine infusion is a popular therapeutic because it has a rapid onset, but the drug has hallucinogenic side effects and the current IV route of administration is impractical for outpatient treatment of pain and depression. There is a great need for alternative and practical methods of ketamine administration and maintenance. Because previous studies have focused primarily on treating either pain or depression, our workshop will introduce participants to a novel treatment for comorbid pain and depression. We will also provide information regarding ketamine maintenance using the sublingual route.

Learning Objectives:

- Acquire knowledge about the novel use of Ketamine in Chronic Pain + Depression.
- Acquire knowledge about the use of sublingual Ketamine for maintenance treatment.

INTRAVENOUS KETAMINE FOR THE TREATMENT OF COMORBID PAIN AND DEPRESSION*

Jonathan Dang, Cedars-Sinai Medical Center, Psychiatry

Individual Abstract: Chronic pain and depression are two of the most debilitating disorders in the Western world, which often coexist in clinic. In patients treated for chronic pain, the prevalence of depression is approximately 18-85%. Similarly, in patients treated with depression, the prevalence of chronic pain is reported to be 51.8-59.1%. It is often that depression and chronic pain are so closely related that distinguishing between which causes which becomes impossible. Currently available conventional antidepressants delay in therapeutic efficacy of several weeks to months and approximately 1/3 of patients respond to these agents and 2/3 will respond only after trying several classes of antidepressants. Likewise, many patients with chronic pain find no success with traditional analgesics such as Effexor, Elavil, Cymbalta, or Nortriptyline. In the search for improved therapies for pain and depression, medications with novel mechanism of actions have been sought. One such promising medication is ketamine- an N-methyl-D-aspartate (NMDA) receptor antagonist. There have been numerous reports on the effectiveness of ketamine as a treatment for depression alone and chronic pain alone but only one study examined ketamine for the treatment of comorbid pain and depression and one study on rat model. Further, the effects of ketamine on chronic pain and depression can be observed within minutes or hours of an initial dose. Because previous studies have focused primarily on treating one condition or the other (chronic pain or depression), the current study will examine the efficacy of ketamine as a treatment for co-morbid chronic pain and depression in medical inpatients.

Learning Objectives:

- To describe the current usage of IV ketamine for the treatment of pain and depression.
- To understand the efficacy of IV ketamine for the treatment of pain and depression.

Literature References:

- Jafarinia, M., Afarideh, M., Tafakhori, A., Arbabi, M., Ghajar, A., Noorbala, A. A., ... & Akhondzadeh, S. (2016). Efficacy and Safety of Oral Ketamine versus Diclofenac to Alleviate Mild to Moderate Depression in Chronic Pain Patients: A Double-Blind, Randomized, Controlled Trial. *Journal of Affective Disorders*.
- Zhang, G. F., Wang, J., Han, J. F., Guo, J., Xie, Z. M., Pan, W., ... & Sun, K. J. (2016). Acute single dose of ketamine relieves mechanical allodynia and consequent depression-like behaviors in a rat model. *Neuroscience Letters*, 631, 7-12.

KETAMINE FOR TREATMENT OF DEPRESSION IN PARKINSON'S DISEASE*

Brigitte Vanle, Cedars-Sinai Medical Center

Individual Abstract: There is a great need for alternative pharmacological methods to treat depression in Parkinson's Disease (PD) patients, as mainstream anti-depression drugs are largely ineffective in the PD population. A major goal in Parkinson's Disease improve the Parkinsonian-related depression and non-motor symptomatology and improve the quality of life in PD patients. PD is the second most common neurodegenerative disorder in the US. PD etiology is likely the result of environmental and genetic stressors; however, there is more evidence for environmental factors as nearly 90% of PD cases are sporadic. In advanced PD, depression symptoms can be severe. Psychiatric-related and depression symptoms are highly relevant symptoms in PD pathology, but can be overlooked when treating the more obvious motor-related symptoms. Current pharmacological treatments for depression such as SSRI's are largely ineffective for the PD population, and there is a critical need to define alternative pharmacological agents and ameliorate depressive symptoms within this patient population. An overview of current PD pharmacological treatments, their advantages and disadvantages will be discussed during this workshop. The use of Ketamine in PD patients is a largely unexplored area. One case report described that a 20-mg dose of Ketamine completely

removed severe tremor and attenuated dyskinesia for perioperative. Interestingly, there is empirical evidence that NMDA antagonists reduce chronic motor symptoms. Additionally, double-blind placebo-controlled studies showed a reduction in L-DOPA induced dyskinesia with NMDA antagonists (ie. amantadine) Additional mechanisms supporting the role of Ketamine in dyskinesias and Parkinsonian-related depression will be further discussed. As an orphan drug, Ketamine provides rapid relief from invasive negative cognitions and reported depressive symptoms. Most patients report symptom remission for days to weeks following single- or brief-multiple-dose infusion treatments. However, current IV route of administration is impractical for outpatient treatment of depression, alternative formulations such as extended release are needed, and although understudied, an intranasal Ketamine route shows promise. At Cedars-Sinai, we propose to conduct a pilot trial assessing the efficacy of a single Ketamine infusion as an augmentation strategy with traditional oral antidepressants. Although Ketamine primarily antagonizes NMDA receptors, other mechanisms supporting the drug's anti-depressive symptoms are currently unclear and need to be further investigated. The current challenges and validation for utilizing Ketamine in PD patients will be thoroughly explored.

Learning Objectives:

- Clearly describe the rationale for the use of Ketamine to treat depression in Parkinson's Disease.
- Describe the clinical utility of Ketamine as an augmentation strategy for antidepressant maintenance.

Literature References:

- Hu, Y. D. et al. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. *Psychol Med* 46, 623-635, doi:10.1017/s0033291715002159 (2016).
- Zarate, C. A., Jr. et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63, 856-864, doi:10.1001/archpsyc.63.8.856 (2006).

THE CHALLENGES OF MAINTENANCE AND RELAPSE PREVENTION AFTER KETAMINE IV: THE ROLE OF SUBLINGUAL KETAMINE*

Waguih IsHak, Cedars-Sinai Medical Center and UCLA

Individual Abstract: Significant progress has been made with acute treatment using ketamine infusions, especially with expanding uses as presented in this symposium. However, maintenance ketamine infusions are limited in practicality due to the expenses associated with the preparation, administration and monitoring. Therefore, an effective continuation therapy to prevent relapse is warranted. This presentation expands on this concept using sublingual ketamine focusing on management and preventing relapse after a single ketamine infusion used to test whether the patient is ketamine responder or not. Bioavailability and side effect profile of sublingual ketamine will be discussed.

Learning Objectives:

- Acquire knowledge about the indications of sublingual Ketamine for maintenance treatment.
- Acquire knowledge about the bioavailability and side effects sublingual Ketamine for maintenance treatment.

Literature References:

- Chong C, Schug SA, Page-Sharp M, Jenkins B, Ilett KF. Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: Preliminary findings from a three-way randomized, crossover study. *Clin Drug Investig.* 2009;29(5):317-24.
- Lara DR, Bisol LW, Munari LR. Antidepressant, mood stabilizing and procognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. *Int J Neuropsychopharmacol.* 2013 Oct;16(9):2111-7.

REDUCING HEALTH DISPARITIES BY PROMOTING FUNCTIONAL AND LIFE-SATISFACTION ASSESSMENTS IN RESEARCH AND CLINICAL PRACTICE: CONSENSUS GUIDELINES TO ENHANCE MEASUREMENT-BASED CARE OF DEPRESSION*

Manish Jha, UT Southwestern Medical Center

Overall Abstract: While practice guidelines for Major Depressive Disorder routinely recommend the measurement-based care (MBC) approach of making systematic treatment decisions based on routine assessments of symptom severity, side-effects, and treatment adherence, its adoption in clinical practice has been limited. Unlike management of other chronic diseases, treatment of depression is often “carved out” from primary care providers and handed over to mental health providers. This results in poor treatment outcomes for depressed patients which disproportionately affects minority and low-income population. There is a severe shortage of mental health professions serving this population; for example, over 80% of the counties in the state of Texas have been designated as mental health provider scarcity area. As treatment outcomes with MBC in primary care settings are comparable to psychiatric setting, universal screening of depression in primary care settings and use of MBC for those who screen positive is a highly effective and efficient way to improve clinical outcomes and reduce health disparities.

The VitalSign6 project at UT Southwestern is one such example of an academic-community partnership that has screened over 30,000 patients from low-income and minority population for depression and enrolled over 3000 previously undiagnosed depressed patients in MBC with their primary care provider. However, recent work from our group and others has demonstrated that exclusive focus on depressive symptom severity in defining treatment outcomes is inadequate. Early changes in function and life-satisfaction have been shown to independently predict short- and long- term treatment outcomes. Additionally, functional and life-satisfaction impairments often persist after symptomatic remission, are associated with worse long-term clinical outcomes, and are subjectively valued to be more important by patients as compared to symptom change. As functional recovery is distinct from symptomatic recovery, we propose that inclusion of function and life-satisfaction measures will enhance MBC approach. However, in contrast to the consensus guidelines to evaluate changes in depression severity with treatment, there are no similar easy-to-interpret recommendations for measuring or conceptualizing changes in function and life-satisfaction. This workshop is intended to generate a discussion among attendees to develop consensus definitions for function and life-satisfaction thresholds and identify how these definitions can be implemented in research and clinical care as well as guide future policy changes. While depression affects multiple dimensions of life, this workshop will focus specifically on functional productivity, both work and non-work related, and 3) life-satisfaction. In three

separate 15-minute presentations, workshop faculty will review impairments reported by depressed patients and independent prognostic effect of early improvement in these domains as well as policy-driven initiatives on improving behavioral health in state of Texas. Based on historical experience that similar workshops have been attended by national and international thought leaders from industry and academia, workshop faculty will lead an engaged discussion of approximately 1-hour to 1) develop consensus recommendations for defining thresholds for impairments in above-mentioned domains, and 2) identify barriers to implementation of functional and life-satisfaction measures in research and clinical practice, with special emphasis on underserved minority population.

Learning Objectives:

- Recognize the need for policy changes to improve treatment outcomes of depressed patients from low-income and minority populations.
- Learn to evaluate changes in function and life-satisfaction with antidepressant treatment and their prognostic significance on long-term clinical course.
- Identify opportunities to integrate functional and life-satisfaction assessments in research and clinical practice.

WORK AND NON-WORK RELATED PRODUCTIVITY IMPROVEMENT WITH ANTIDEPRESSANT MEDICATIONS PREDICTS LONG-TERM CLINICAL OUTCOMES IN OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER*

Tracy Greer, UT Southwestern Medical Center

Individual Abstract: Major Depressive Disorder (MDD) significantly impacts performance of both work and non-work related routine daily activities. We have shown that work productivity is significantly impaired in employed MDD patients but the extent of impairments in non-work related routine activities and its association with antidepressant treatment and long-term clinical outcomes has not been established.

Activity impairment was measured with the sixth item of Work Productivity and Activity Impairment Scale in the Combining Medications to Enhance Depression Outcomes trial (n=665). Published norms were used to define activity impairment levels. The relationship between baseline activity impairment and sociodemographic and clinical characteristics as well as changes in activity impairment and other clinical outcomes over course of treatment were evaluated. Remission status at 3 and 7 months were predicted based on activity impairment level at week 6.

Higher psychosocial function impairments and number of comorbid medical conditions were associated with greater activity impairment at baseline. Proportion of participants with severe activity impairment declined from 47.6% at baseline to 18.7% at 3 months, and mean activity impairment decreased from 57.1 at baseline to 32.8 at 3 months. During course of treatment, levels of activity impairment correlated most strongly with psychosocial function among measures of symptom severity, function, quality of life, and side-effect burden. No or minimal activity impairment at week 6 was associated with 2-3 times higher rates of remission at 3 and 7 months as compared to moderate or severe activity impairment levels even after controlling for remission status at week 6 and select baseline variables.

Depressed patients have high levels of non-work related activity impairment at baseline that improves significantly with treatment and independently predicts long-term clinical

outcomes. Brief systematic assessment of activity impairment during the course of antidepressant treatment can help inform clinical decision making.

Learning Objectives:

- Depressed patients report significant impairment in their work and non-work related day to day activities.
- Early normalization of productivity by week 6 is independently associated with substantially higher likelihood of remission after 3 and 7 months of treatment.

Literature References:

- Jha MK, Minhajuddin A, Greer TL, Carmody T, Rush AJ, Trivedi MH. Early Improvement in Work Productivity Predicts Future Clinical Course in Depressed Outpatients: Findings From the CO-MED Trial. *The American journal of psychiatry*. 2016;appiajp201616020176.
- Trivedi MH, Morris DW, Wisniewski SR, Lesser I, Nierenberg AA, Daly E, Kurian BT, Gaynes BN, Balasubramani GK, Rush AJ. Increase in work productivity of depressed individuals with improvement in depressive symptom severity. *The American journal of psychiatry*. 2013;170:633-641.

CHANGES IN LIFE-SATISFACTION WITH ANTIDEPRESSANT TREATMENT PREDICT LONG-TERM CLINICAL OUTCOMES*

Manish Jha, UT Southwestern Medical Center

Individual Abstract: Major Depressive Disorder is common, often recurrent and/or chronic. Assessing life-satisfaction in addition to the current practice of assessing depressive symptoms has the potential to offer a more comprehensive evaluation of the effects of treatment interventions and course of illness. Depressed patients who continue to report impaired life-satisfaction after responding to antidepressant treatment may be at higher risk of future symptomatic worsening. Conversely, depressed patients who experience early improvement in life-satisfaction have higher rates of long-term remission.

This presentation will include findings from two large-scale studies, the Continuation Phase Cognitive Therapy Relapse Prevention and the Combining Medications to Enhance Depression Outcomes trial. In both studies, over two thirds of depressed patients continued to experience impaired life-satisfaction after acute-phase antidepressant treatment. Patients who experienced early normalization of life-satisfaction by week 4 were three to six times more likely to be in remission by 3 and 7 months. Conversely, depressed patients who continued to experience impaired life-satisfaction were two times more likely to relapse over a follow-up period of up to three years.

Learning Objectives:

- Depressed patients who report impaired life-satisfaction even after symptomatic remission have two times higher rates of relapse over 3 year follow-up period.
- Normalization of life-satisfaction by 4-week is associated with 3-6 times higher remission rates at 3 and 7 months.

Literature References:

- Jha MK, Minhajuddin A, Thase ME, Jarrett RB. Improvement in self-reported quality of life with cognitive therapy for recurrent major depressive disorder. *J Affect Disord*. 2014;167:37-43.

- Jha MK, Greer TL, Grannemann BD, Carmody T, Rush AJ, Trivedi MH. Early normalization of Quality of Life predicts later remission in depression: Findings from the CO-MED trial. *J Affect Disord.* 2016;206:17-22.

POLICY IMPLICATIONS FOR TREATMENT OUTCOMES OF DEPRESSED PATIENTS FROM LOW-INCOME AND MINORITY POPULATIONS

Michele Guzman, Meadows Mental Health Policy Institute

Individual Abstract: The Meadows Mental Health Policy Institute (MMHPI/Institute) is a non-profit organization established in 2013 to provide policy research and development to improve mental health services in Texas. It analyzes, evaluates, and develops public policy at the state and local levels through evidence-based research and data-driven project evaluation. A key interest for the Institute is to reduce health disparities, which is especially amplified for mental health services in the state of Texas due to scarce public sector provisions. According to the Centers for Disease Control and Prevention and large scale epidemiologic studies, nearly 8% of people age 12 or older report current depression. People living below the poverty level are 2.5 more likely to have depression. Black and Hispanic individuals have higher rates of mild and moderate depressive symptoms than non-Hispanic white persons. Of those experiencing any depression, nearly 43% report serious functional challenges in home, work, and social activities. To reduce the health disparities, MMHPI supports efforts to include mental health screening and treatment in primary care settings. The Collaborative Care model is one such model that has had very positive outcomes and has been demonstrated to produce benefits greater than the costs of such a program with a total positive impact (to taxpayers, participants, and others) of \$5,870 per participant for labor market earning associated with major depression and \$7,304 overall. The other successful model in state of Texas is the VitalSign6 project which has focused on patient-primary care provider relationship to minimize the need for external referrals and improve depression outcomes in primary care settings. The Institute helped convene a meeting in 2016 on cross-systems collaboration which was headed by Dr. Madhukar Trivedi and included Chairs from Departments of Psychiatry at medical centers across the state. Additionally, MMHPI team members have been working with the Texas Business Group on Health to inform employers, insurers, and other claims payers about effective treatment for depression. On the legislative front, the Institute is examining a possible pathway to strengthen adolescent mental health screenings for youth ages 12-18 to detect depression and other conditions earlier.

Learning Objectives:

- Recognize the need for policy changes to improve treatment outcomes of depressed patients from low-income and minority populations.
- Examine the types of policy changes needed to provide greater access to screening and treatment for depression.

Literature References:

- Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015; 386(9995):743-800.
- Harding KJ, Rush AJ, Arbuckle M, Trivedi MH, Pincus HA. Measurement-based care in psychiatric practice: a policy framework for implementation. *The Journal of clinical psychiatry.* 2011;72:1136-1143.

TARDIVE DYSKINESIA: THE FORGOTTEN ADVERSE EVENT*

Jean-Pierre Lindenmayer, New York University

Overall Abstract: Tardive dyskinesia (TD) is a neurological condition characterized by involuntary movements of the orofacial region (ie, tongue, lips, jaw, face) and choreo-athetoid movements of the limbs and trunk. Most often TD emerges after long-term first-generation antipsychotic (FGAs) treatment over months to years, however, second-generation antipsychotics (SGAs) may also be involved, and often TD persists after discontinuation of the offending medication. Other risk factors for TD appear to include older age, higher antipsychotic dose, Parkinsonism, schizophrenia and cognitive impairment (Margolese et al., 2005). While often of mild intensity, moderate to severe TD can be disabling. Most patients with mild TD are unaware of their involuntary movements and do not seek treatment (Macpherson and Collis, 1992). Several questions remain unresolved about this debilitating adverse event: There appears to have been a decrease of the incidence of TD with the use of SGAs, but the data are not clear (Hsieh et al – in press). This may be due to under-diagnosing of TD among younger psychiatrists who have not been trained in recognizing TD symptoms. SGAs may present a lesser risk for TD or be associated with milder forms of TD compared to FGAs, the dosing of SGAs may be overall lower than that of FGAs in the past. Further, the pathophysiology of TD is still not fully understood, and, finally, there is no FDA approved treatment available yet, although the exploration of a novel mechanism involving the highly selective inhibitor of the vesicular monoamine transporter 2 (VMAT2) has opened new therapeutic possibilities. This Workshop will explore some of these challenges together with possible solutions. The first presentation by Dr. Christoph Correll will focus on the present day prevalence and incidence risk of TD, particularly focusing on the risk in the context of treatment with SGAs. The second presenter, Dr. Jean-Pierre Lindenmayer, will present data on the training level of psychiatric residents and on approaches on how to re-familiarize residents with the signs and symptoms of TD. The third presentation, by Dr. Leslie Citrome, will discuss currently available treatments, including tetrabenazine and the role of the transporter protein vesicular monoamine transporter 2 (VMAT2). The fourth presenter, Dr. Ira Glick, will present data on recent treatment trials of TD with VMAT2 inhibitors such as deuterated tetrabenazine and valbenazine together with clinical implications.

Learning Objectives:

- Participants will be able to better evaluate the current incidence risk of TD with second generation antipsychotics.
- Participants will become familiar with a novel treatment mechanism of TD, the inhibition of VMAT2.

Literary References:

- MacPherson R. and Collis R. Tardive Dyskinesia: Patients' lack of awareness of movement disorder. *Br J of Psychiatry*. 1992 Jan 160; 110-112
- Margolis H, Chouinard G, Kolivakis T, Beauclair L, Miller R. Tardive Dyskinesia in era of Typical and Atypical Antipsychotics. Part 1: Pathophysiology and Mechanisms of Injunction *Can J Psychiatry*. 2005; 50; 541-547
- Hsieh CH, Correll CU, Kane JM, Carbon M. Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis. *J Clin Psychiatry*. – in press.

WHAT IS THE CURRENT PREVALENCE AND INCIDENCE OF TARDIVE DYSKINESIA?*

John Kane, The Zucker Hillside Hospital

Individual Abstract: Objective: Tardive dyskinesia (TD) rates with second-generation antipsychotic (SGA) treatment were estimated to be considerably lower than with first-generation antipsychotics (FGAs). As recent data have questioned this notion, we conducted updated meta-analyses on TD prevalence and incidence.

Method: We conducted an electronic data-base search without language restriction using (“tardive dyskinesia” OR tardive) AND (antipsychotic*) plus specific names of FGAs or SGAs searching for studies conducted since 2000 (time period when both SGAs and FGAs were prescribed) reporting on a) prevalence rates of TD with FGAs or SGAs, or b) on incidence rates of TD in randomized controlled trials (RCTs) comparing SGA to FGA treatment.

Results: The dataset on TD prevalence included 41 studies (n=11,493, age=42.8 years, male=66.4%, schizophrenia-spectrum disorders=77.1%). The global mean TD prevalence was 25.3% (95%CI=22.7-28.1%), varying greatly. TD prevalence was lower with current SGA vs FGA treatment (20.7%; 95%CI=16.6-25.4% vs 30.0%; 95%CI=26.4-33.8%, p=0.002). This difference remained significant after controlling for moderators: higher age (p=0.004); region (Asia vs. Europe, p=0.12; Asia < USA, p=0.009; Asia < other regions, p=0.015). Additional moderators of TD prevalence included longer illness duration (p=0.03) and frequency of parkinsonism (p=0.017). Particularly low TD prevalence was found in the treatment arms with FGA-naïve subjects, relative to SGA-treated cohorts with likely prior FGA exposure (7.2% vs 23.4%; p<0.001). The still preliminary dataset on TD incidence in RCTs included 26 studies (n=9157, age=38.7 years, male=65.1%, 23 of 26 studies including schizophrenia-spectrum disorders; mean study duration=1.6 years). Treatment-emergent TD was observed in 132 of 5937 patients treated with SGAs (2.2% in 4380 person years) and in 203 of 3220 patients treated with FGAs (6.3% in 1982 person years). Annualized TD rates were significantly lower with SGAs relative to FGAs (rate ratio (RR)=0.37; CI=0.28-0.48; p<0.0001). The dose of the FGA comparator (below vs. above 500mg chlorpromazine equivalent), did not significantly moderate this difference (p=0.29). Similarly, the FGA-SGA TD rate ratios did not differ between SGA subgroups and persisted independently within each subgroup (all comparisons p<0.01). Moreover, the segregation of TD rates persisted regardless of the case definition used in the study (Schooler-Kane criteria vs. other TD reporting criteria) and regardless of study design (double-blind vs. open label). However, FGA-SGA TD RRs differed significantly depending on the study sponsor (industry vs. academic, p=0.004). Nevertheless, RR differences independently persisted within each subgroup (academic studies: mean RR=0.53; CI=0.38-0.74; p<0.0001; industry sponsored studies: mean RR=0.27; CI=0.20-0.37; p<0.001). Moderator analyses for age, sex, illness duration, study region and anticholinergic use were non-significant. Acquisition of unpublished data is ongoing and may change the final results.

In both meta-analyses, reports on TD severity, provided by few studies, were of insufficient quality for meta-analysis.

Conclusions: Both the meta-analysis of TD prevalence and TD incidence rates in RCTs confirmed the lower TD risk with SGAs versus FGAs. Contrasting to earlier suggestions, this advantage was not driven by studies that used high dose FGA comparators. Rating scale-based TD remains highly prevalent even in the era of predominant SGA treatment, yet, prior

exposure to FGAs may partly be one reason for this. TD severity was insufficiently reported to evaluate if TD expression has become more subclinical.

Learning Objectives:

- Review the Evolution of Tardive Dyskinesia Prevalence with First- and Second-Generation Antipsychotics.
- Review the Evolution of Tardive Dyskinesia Incidence with First- and Second-Generation Antipsychotics.

Literature References:

- Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis. *J Clin Psychiatry*. – in press.
- Correll CU, Leucht S, Kane JM: Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of one-year studies. *Am J Psychiatry* 2004;161(3):414-425.

DO PSYCHIATRIC RESIDENTS UNDERRECOGNIZE TARDIVE DYSKINESIA?*

Jean-Pierre Lindenmayer, New York University

Individual Abstract: Tardive Dyskinesia is a neurological condition characterized by irreversible involuntary movements of the orofacial region (ie, tongue, lips, jaw, face) and choreo-athetoid movements of the limbs and trunk. Most often TD emerges after long-term first-generation antipsychotic (FGAs) treatment over months to years, however, second-generation antipsychotics (SGAs) may also be involved, and often TD persists after discontinuation of the offending medication. There appears to have been a decrease of the incidence of TD with the use of SGAs. In one recent study the prevalence of TD with FGAs was reported to be 20.8 % (Ryu et al, 2015), while the rate for exclusive treatment with SGAs was 5.0%, however the data are not clear. Another finding was that TD with SGAs may be of a lesser severity. This possible decrease may be due to a real lesser risk of SGAs in the contribution to TD SGAs or SGAs may be associated with milder forms of TD compared to TDs seen with FGAs. In addition, the dosing of SGAs may be overall lower than that of FGAs in the past. or possibly to the under-diagnosing of TD. Another reason may be that younger psychiatrists who have not been trained in recognizing TD symptoms and that have been exposed predominantly to the treatment with SGAs may not recognize symptoms of TD. Method: In order to explore this possibility we collected data from three sources: 1. We sent a questionnaire to 13 psychiatric residents in their 4th year of training in an academic residency program presenting them with 20 questions on questions about prevalence rates, risk factors, symptom presentation and treatment for TD patients. 2. We sent the same questionnaire to 25 psychiatrists treating acute and chronic in- and outpatients and with an average of >5 years of post-residency clinical experience. A “passing” grade was given if 80 % of the questions were answered correctly. 3. We presented two patients with mild TD within a series of 5 videotaped patient interviews to 13 psychiatric residents in their 4th year of training asking them to make a psychiatric diagnosis and to also diagnose any movement disorder. Results: 1. Questionnaire data was returned by 96 % of the residents. Only 45 % of the residents attained a passing grade. 2. Questionnaire data was returned by 75 % of the psychiatrists. A passing grade was attained by 68 % of the respondents. 3. A correct diagnosis of TD of both videotaped cases was made by 60 % of the queried psychiatric residents. Conclusions: There appeared to be lower level of clinical knowledge fund on TD and its treatment in senior psychiatric residents as compared to established psychiatrists. Residents tended to miss the

milder cases of TD pointing to an underrecognition of TD and to the need for additional training. Such training interventions can include (1) videotaped case presentations particularly of mild and moderate TD patients, (2) demonstration of the complete AIMS examination by an experienced clinician and (3) exposure to patients with TD in residents' clinical rotations.

Learning Objectives:

- Participants will learn about the need for additional training in movement disorders and TD in psychiatric residents.
- Participants will learn about effective teaching strategies of movement disorders for psychiatric residents.

Literature References:

- Correll CU, Schenk EM: Tardive dyskinesia and new antipsychotics. *Current Opinion in Psychiatry* 2008, 21:151–156
- Hansen TE, Brown WL, Weigel RM, Casey DE. Underrecognition of Tardive Dyskinesia and drug-induced Parkinsonism by psychiatric residents. *Am J Psychiatry* 1992,14:340-344

TREATMENT LANDSCAPE OF TARDIVE DYSKINESIA: WHAT WORKS, WHAT DOESN'T, AND WHY*

Leslie Citrome, New York Medical College

Individual Abstract: The pathophysiology of tardive dyskinesia is complex. On one level, chronic high levels of dopamine antagonist medications may "starve," and subsequently up-regulate, dopamine receptor number and responsiveness so that randomly available dopamine molecules may initiate abnormal involuntary movements in a hyper-sensitive system. Also contributory are possible abnormalities of striatal GABA neurons and degeneration of striatal cholinergic interneurons. Other theories have included oxidative stress created from chronic antipsychotic use. Genetic vulnerability may also be a factor in that tardive dyskinesia has been associated with several different polymorphisms of dopamine receptor genes, the dopamine transporter gene, and the manganese superoxide dismutase gene.

As of 2016 there are no approved treatments for tardive dyskinesia and preventive principles are recommended such as ensuring that antipsychotic medication is truly indicated, using conservative maintenance doses, using atypical antipsychotics instead of conventional antipsychotics, and regular monitoring using the Abnormal Involuntary Movement Scale. Should tardive dyskinesia develop, management strategies have included the use of atypical antipsychotics in patients who have experienced tardive dyskinesia with conventional antipsychotic agents. Novel management strategies include tetrabenazine, currently the "off-label" treatment of choice for moderate to severe forms of tardive dyskinesia, but other potential interventions include reserpine, Vitamin E, melatonin, vitamin B6, donepezil, and branched chain amino acids, however evidence for these interventions is uneven in quality and robustness. Other off-label interventions found to be potentially helpful as per the American Academy of Neurology include clonazepam and ginkgo biloba, as well as possibly amantadine; found not helpful are diltiazem, galantamine and eicosapentaenoic acid. Surgical interventions are a last resort, for example deep brain stimulation of the globus pallidus interna and lesioning surgeries such as pallidotomy.

Tetrabenazine is a reversible and specific inhibitor of vesicular monoamine transporter-2 (VMAT-2), a transporter that packages neurotransmitters (preferentially dopamine) into

vesicles for release into the synapse. As such, VMAT-2 inhibitors are a focus of current drug development in an effort to design an intervention that is as efficacious as tetrabenazine, but that does not carry the same limitations, namely significant side effects, short half-life, and drug-drug interactions.

Learning Objectives:

- To be aware of current pharmacological treatment options for tardive dyskinesia.
- To understand how tetrabenazine (and its variants) can reduce the symptoms of tardive dyskinesia.

Literature References:

- Margolese HC, Chouinard G, Kolivakis TT, Beauclair L, Miller R, Annable L. Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 2: Incidence and management strategies in patients with schizophrenia. *Can J Psychiatry*. 2005;50(11):703-14.
- Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics*. 2014;11(1):166-76.

NEW PHARMACOLOGIC INTERVENTIONS FOR TARDIVE DYSKINESIA: AN UPDATE*

Ira Glick, Stanford University School of Medicine

Individual Abstract: There are two novel compounds being currently developed for the treatment of TD. Deutetrabenazine (SD-809) and valbenazine (NBI-98854) are two medications in Phase III of clinical development for the treatment of tardive dyskinesia (TD). Tetrabenazine is an “orphan drug” for the treatment of Huntington’s disease that is also used to treat TD “off-label.” The mechanism of action of tetrabenazine is by inhibiting the vesicular monoamine transporter 2 (VMAT-2), resulting in depletion of synaptic dopamine. Unfortunately, its pharmacokinetic profile requires frequent dosing. Deutetrabenazine and valbenazine are alternatives to tetrabenazine and are also VMAT-2 inhibitors. Deutetrabenazine differs from tetrabenazine in that deuterium atoms take the place of hydrogen atoms on the molecule, thus slowing metabolism, allowing less frequent dosing, and improving tolerability. A successful Phase II/III, randomized, double-blind, placebo-controlled, parallel-group study in patients with tardive dyskinesia was completed, where 117 patients with moderate to severe TD were randomized to either twice-daily deutetrabenazine or placebo for a total of 12 weeks. Deutetrabenazine was statistically significantly superior to placebo on the primary efficacy endpoint in change of central AIMS ratings. For patients with a baseline AIMS score ≥ 6 , categorical improvement, as measured by a score of “very much improved” or “much improved” on either the CGI-I or the Patient Global Impression of Change, was greater for deutetrabenazine than for placebo, 52.1% vs 34.7% and 45.8% vs 28.6%, respectively, resulting in NNTs of 6 vs placebo for each measure. Treatment with deutetrabenazine did not result in any reports of depression or suicidal ideation. Other trials for deutetrabenazine are in progress, including another 12-week randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study of patients with moderate to severe TD and an open-label, 54-week safety study in patients with moderate to severe TD. Valbenazine is a new molecular entity that is metabolized to an active derivative (+)- α -dihydro-tetrabenazine. In a randomized, 6-week, double-blind, placebo-controlled, dose-titration Phase II study, once-daily valbenazine significantly improved tardive dyskinesia and was well tolerated. Responder rates (defined as a $\geq 50\%$ improvement in the AIMS score) were 48.9% for valbenazine vs 18.2% for placebo, resulting in a NNT of 4. CGI-I scores of

“very much improved” or “much improved” were observed in 66.7% vs 15.9% of participants randomized to valbenazine and placebo, respectively, for a NNT of 2. Also available are the results of a 6-week Phase III study where valbenazine was superior to placebo on change of the AIMS total score with a large effect size (Cohen’s $d = 0.90$). The latter compound is currently being reviewed by the FDA.

Learning Objectives:

- To understand alternatives to tetrabenazine for the treatment of tardive dyskinesia.
- To distinguish the similarities and differences between deutetabenazine (SD-809) and valbenazine (NBI-98854).

Literature References:

- Citrome L. Emerging Pharmacological Therapies in Schizophrenia: What’s New, What’s Different, What’s Next? *CNS Spectrums* (in press)
- O’Brien CF, Jimenez R, Hauser RA, et al. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *Mov Disord.* 2015; 30(12): 1681–1687

Thursday, June 1, 2017

8:15 a.m. - 9:45 a.m.

Keynote Plenary

KEYNOTE PLENARY SESSION*

Marlene Freeman, Massachusetts General Hospital

Overall Abstract: This Keynote Plenary Session will address disparities and opportunities in treatment engagement across diverse populations, dovetailing with the 2017 ASCP annual meeting theme. Dr. Roberto Lewis-Fernández will address disparities in psychopharmacology among racial and ethnic minorities. He will present data regarding interventions to overcome specific challenges regarding the barriers at the patient, provider, and organizational level. Dr. Michael Compton will address the societal approaches to disparities, and discuss health promotion policy optimization and social variables. Dr. Andrew Nierenberg will discuss opportunities for patient engagement in research in psychopharmacology and clinical trial methodology. He will discuss the federally funded Mood Disorders Patient Powered Research Network and the Institute of Medicine’s concept of a learning health system.

OVERCOMING DISPARITIES IN TREATMENT ENGAGEMENT ACROSS DIVERSE POPULATIONS*

Roberto Lewis-Fernández, College of Physicians & Surgeons, Columbia University

Abstract: Treatment engagement – defined as treatment initiation, participation, adherence, and retention – can be problematic among all population groups, but racial/ethnic minorities in the US face substantial disparities in this area, especially with respect to psychopharmacotherapy. Engagement barriers affecting this population over and above the typical barriers exist at the patient, provider, and organizational level. They include higher stigma,

limited health literacy, mismatched expectancies and communication styles during the session, lack of appropriate language services, and higher use of guideline-discordant care. Interventions have been developed at each of these levels to help overcome these engagement disparities based on the principles of cultural and structural competence. This talk will present several of these interventions and discuss their evidence base.

Learning Objectives:

- Identify treatment engagement disparities affecting racial/ethnic minorities in the US.
- Describe interventions designed to overcome these disparities at patient, provider, and organizational levels.

Literature References:

- Interian A, Lewis-Fernández R, Dixon L: Improving treatment engagement of underserved US racial-ethnic groups: A review of recent interventions. *Psychiatric Services* 2013; 64:212-222.

THE SOCIAL DETERMINANTS OF MENTAL HEALTH: WHAT? WHO? AND HOW?*

Michael Compton, Columbia University, College of Physicians & Surgeons

Abstract: Social and environmental factors affect risk for mental illnesses and substance use disorders, as well as health outcomes of persons with these disorders. Such factors, in addition to their independent and combined effects, can also influence genetic determinants of health and illness through gene-by-environment interactions and epigenetic mechanisms. These factors clearly have an effect at the individual level and should be a focus of intervention in the clinical setting. However, the social determinants of health (and the social determinants of mental health) exert their effects more broadly at the societal level and thus can be most effectively addressed through changes in public policies and social norms. Specifically, the social determinants of mental health are understood as being underpinned by unequal distribution of opportunity and, more deeply, by public policies (e.g., legislation that may not specifically pertain to health but ultimately has far-reaching effects on health) and social norms (e.g., cultural opinions and biases that set the stage for poorer health among disadvantaged groups). The greatest population-based impact for improving mental health and reducing risk of mental illnesses and substance use disorders will be achieved by optimizing public policies to make them more health promoting, and by altering social norms so that the health of all members of society is a priority.

Learning Objectives:

- Define the concept of the social determinants of health and discuss this concept's link to the concept of social justice.
- List five social determinants of health with known associations with mental health.
- Describe three ways in which psychiatrists and other mental health professionals can be involved in addressing the social determinants of mental health in order to decrease risk for behavioral health disorders.

Literature References:

- Compton MT, Shim RS (2015) The social determinants of mental health. *FOCUS*, 13:419–425.

PEOPLE/PARTICIPANTS/PATIENTS AT THE CENTER: RE-ENGINEERING PSYCHOPHARMACOLOGY TRIALS*

Andrew Nierenberg, Massachusetts General Hospital

Abstract We have an opportunity to re-engineer how we do clinical trials in psychopharmacology. Our current structure is to have researchers as the hubs and participants connected to the researchers by spokes. Researchers are at the center - they conceive, plan, and execute the study. Participants follow directions. Researchers spend a lot of resources searching for participants. Potential participants usually do not search for researchers. Researchers publish and never find out the actual impact of their work on clinical practice - citations and academic promotions? Yes - Evidence for changes in outcomes in the real world? generally no. Participants rarely, if ever, find out about the results or outcome of the study. Participants rarely become engaged in the business of research. The Patient Centered Outcomes Research Institute (PCORI) has developed a network to put people/participants/patients back into the center. The ultimate goal is develop a true Learning Health Care System with patients, researchers, clinicians, and administrators and people from Pharma collaborating to not only plan and conduct research which matters, but also to engage all stakeholders so that the results of the research can be put into clinical practice and then the system can assess if health outcomes are better. This presentation will review the Institute of Medicine concept of a learning healthcare system, the state of the PCORI network (soon to be named the People-Centered Research Foundation), and a path forward to engage people/participants/patients from the design to implementation phases along with clinicians to recruit and randomize at the point-of-care.

Learning Objectives:

- The participants will know what an ideal learning healthcare system is and understand how to engage stakeholders in clinical trials.

Literature References:

- The study is open: Participants are now recruiting investigators. Terry S. *Sci Transl Med.* 2017 Jan 4;9(371).
- Data Acquisition, Curation, and Use for a Continuously Learning Health System. Krumholz HM, Terry SF, Waldstreicher J. *JAMA.* 2016 Oct 25;316(16):1669-1670.
- Transforming Evidence Generation to Support Health and Health Care Decisions. Califf RM, Robb MA, Bindman AB, Briggs JP, Collins FS, Conway PH, Coster TS, Cunningham FE, De Lew N, DeSalvo KB, Dymek C, Dzau VJ, Fleurence RL, Frank RG, Gaziano JM, Kaufmann P, Lauer M, Marks PW, McGinnis JM, Richards C, Selby JV, Shulkin DJ, Shuren J, Slavitt AM, Smith SR, Washington BV, White PJ, Woodcock J, Woodson J, Sherman RE. *N Engl J Med.* 2016;375(24):2395-2400.
- The Patient-centered Outcomes Research Institute's Role in Advancing Methods for Patient-centered Outcomes Research. Fleurence R, Whicher D, Dunham K, Gerson J, Newhouse R, Luce B. *Med Care.* 2015;53(1):2-8.4.
- Improving the care of patients who have treatment-resistant depression: the promise of the PCORnet Mood Network. Nierenberg AA, Sylvia L, Doederlein A, Edgman-Levitan S, Muskin A, Jewell L, Walker M, Goodman D, Farahbakhsh M, Hearing C, Tovey R, Deckersbach T. *J Clin Psychiatry.* 2015 Apr;76(4):e528-30.

10:00 a.m. - 12:30 p.m.

Federal Agency Directors Plenary

**of special interest to clinicians*

FEDERAL AGENCY DIRECTORS PLENARY SESSION

Mark Rapaport, Emory University School of Medicine

Overall Abstract: Dr. Raye Litten will discuss recent advances and long-term goals of the medications development program at NIAAA. Dr. Amir Tamiz will cover NINDS research priorities and funding opportunities to support translational and clinical neuroscience research. Dr. Josh Gordon will present an update on activities and priorities at the NIMH. Dr. Kevin Walton, representing NIDA, will provide an overview of electronic cigarettes, the potential role they may play in treatment for smoking cessation, and the efforts NIDA is taking to understand the device's risks and benefits. Dr. Richard Nakamura, Ph.D., Director of the NIH Center for Scientific Review (CSR) will provide an update on recent changes affecting review of NIH grant applications. Dr. Gray Norquist will present current funding initiatives at PCORI and provide an overview of recently funded studies in mental health. Finally, COL Dennis McGurk will address the Department of Defense's research interest in the development of psychopharmacologic interventions addressing Post Traumatic Stress Disorder (PTSD), Suicidality, Depression, and Substance abuse.

NIAAA UPDATE

Raye Litten, NIAAA

Individual Abstract: Raye Litten will discuss recent advances and long-term goals of the medications development program at NIAAA. New initiatives will be highlighted to accelerate the translation of candidate compounds through the drug development pipeline. These include 1) discovering new druggable molecular targets; 2) bridging the gaps in the drug development process; 3) developing, validating, and implementing screening models for testing candidate compounds; 4) enhancing the efficiency of alcohol clinical trials; and 5) improving the methodology of alcohol clinical trials focusing on new endpoints.

Learning Objectives:

- Learn the long-range goals in the discovery, development, and adoption of medications to treat alcohol use disorder.
- Review the new initiatives to advance the medications development program at NIAAA.

Literature References:

- Litten RZ, Falk DE, Ryan ML, Fertig JB (2016) Discovery, development, and adoption of medications to treat Alcohol Use Disorder: Goals for the Phases of Medications Development. *Alcohol Clin Exp Res* 40:1368-1379

NINDS UPDATE

Amir Tamiz, NINDS Division of Translational Research

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

Learning Objectives:

- The objective is to learn about translational efforts within NINDS and priority programs.

Literature References:

- Meghan Mott & Walter Koroshetz. 2015. Bridging the Gap in Neurotherapeutic Discovery and Development: The Role of the National Institute of Neurological Disorders and Stroke in Translational Neuroscience. *Neurotherapeutics* 12:651–654

AN UPDATE FROM THE NIMH

Josh Gordon, National Institute of Mental Health

Individual Abstract: Dr. Gordon will present an update on activities and priorities at the NIMH. The NIMH aims for a balanced portfolio with short, medium and long-term payoffs. Current priorities include suicide prevention, neural circuit technology, and computational and theoretical approaches to psychiatry.

Learning Objectives:

- Attendees will learn about priorities in the near future for research and development of new therapies for psychiatric disorders.

Literature References:

- Gordon JA. On being a circuit psychiatrist. *Nat Neurosci.* 2016 Oct 26;19(11):1385-1386.

NIDA UPDATES

Kevin Walton, National Institute on Drug Abuse

Individual Abstract Kevin Walton, representing NIDA, will provide an overview of electronic cigarettes, the potential role they may play in treatment for smoking cessation, and the efforts NIDA is taking to understand the device's risks and benefits.

Learning Objectives:

- The participant will learn NIDA's efforts to understand the risks and benefits of electronic cigarettes.

NIH CENTER FOR SCIENTIFIC REVIEW - UPDATE

Richard Nakamura, National Institutes of Health

Individual Abstract Richard Nakamura, Ph.D., Director of the NIH Center for Scientific Review (CSR) will provide an update on recent changes affecting review of NIH grant applications. This will help applicants understand the factors influencing success rates and individual awards.

Learning Objectives:

- Learn about recent changes in the NIH Peer Review process for grant applications.

RESEARCH FUNDING IN MENTAL HEALTH AT PCORI

Gray Norquist, Emory Dept. of Psychiatry and Behavioral Sciences

Individual Abstract: This presentation will present current funding initiatives at PCORI and provide an overview of recently funded studies in mental health.

Learning Objectives:

- Participants should learn the funding interests of PCORI.

Literature References:

- The best reference is the link to our funding site: www.pcori.org/funding-opportunities

DOD UPDATES

COL Dennis McGurk, Department of Defense

Individual Abstract: This presentation will address the Department of Defense's research interest in the development of psychopharmacologic interventions addressing Post Traumatic Stress Disorder (PTSD), Suicidality, Depression, and Substance abuse. The brief will include a short overview of the United States Army Medical Research and Materiel Command (MRMC) and Military Operational Medicine Research Program (MOMRP), including overarching research interests and those specific to the Psychological Health Research Program. A review of identified research gaps and recent or ongoing pharmacologic research efforts, research funding opportunities and processes, as well as a short description of our upcoming State of the Science meeting addressing the development of pharmacologic treatments for PTSD will also be covered.

Learning Objectives:

- What areas are of primary interest to DoD relative to the development of pharmacologic solutions for psychiatric treatment? What are some of the special considerations and characteristics that development efforts would need to include in association with their intended use in an active duty military population?
- Demonstrate familiarity with the various funding opportunities available through DoD and how to locate and pursue them.

2:00 p.m. – 3:30 p.m.

Psychopharmacology State-of-the-Art Updates

PSYCHOPHARMACOLOGY STATE-OF-THE-ART UPDATES

Holly Swartz, University of Pittsburgh

Overall Abstract: The purpose of this symposium is to provide an overview of the recent advances in clinical psychopharmacology leading to the development of novel treatments for mood disorders. The session will focus on schizophrenia, anxiety disorders, and neuromodulation.

SCHIZOPHRENIA: WHAT'S NEW IN 2017?*

Nina Schooler, SUNY Downstate Medical Center

Individual Abstract: New anti-psychotic medications continue to be approved for use by the FDA in a steady stream that began with clozapine in 1990. Since then, 15 oral medications have been approved for treatment of schizophrenia and four of those have long-acting formulations in two cases more than one long-acting formulation. There is a vast literature, including meta-analyses, that has addressed questions regarding the efficacy, effectiveness and acceptability of these medicines that go beyond the data generated in order to gain approval and therefore the ability to gain a niche in the treatment armamentarium. This presentation will consider some examples of that literature.

**of special interest to clinicians*

A further effort in psychopharmacological treatment in schizophrenia and psychosis has been directed toward development of medications to treat aspects of schizophrenia that may not be addressed by marketed antipsychotic medications; namely negative symptoms and cognitive impairment. Although cognitive impairment is not recognized in the diagnosis of schizophrenia it is widely recognized as prominent in many if not all patients. The second part of the presentation will report on recent developments in this area.

Tardive dyskinesia, once viewed as being of epidemic proportions and concern in the treatment of patients receiving antipsychotic medications, has receded from clinical and public concern with the advent of the post-clozapine antipsychotic medications. The last and final part of the presentation will provide an update on new developments in treatment of tardive dyskinesia.

Learning Objectives:

- Attendees will recognize the range of evidence available to evaluate the effectiveness of antipsychotic medication for treatment of schizophrenia.
- Attendees will learn about treatments for negative symptoms and cognitive impairment.
- Attendees will recognize the current prevalence of tardive dyskinesia and possible treatment for it.

Literature References:

- Leucht S, Cipriani A, Spinelli L et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013;382:951-962.
- Németh G, Laszlovszky I, Pál Czobor et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet* 2017 on line
- Hauser RA, Factor SA, Marder SR et al. KINECT 3: a randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *American J Psychiatry* 2017 In Press

UPDATE ON THE ANXIETY DISORDERS*

Mark Pollack, Rush University Medical Center

Individual Abstract: Although there are a variety of effective pharmacologic and psychosocial therapeutics for the anxiety disorders, many patients remain symptomatic despite treatment. This presentation will review some recent developments in the pharmacotherapy of the anxiety disorders including approaches to refractory anxiety conditions, and discuss the application of insights from translational neuroscience that have shaped novel attempts to pharmacologically enhance the efficacy of cognitive-behavioral therapy.

Learning Objectives:

- To understand the recent application of psychopharmacological therapeutics for the anxiety disorders.

Literature References:

- Pollack MH, VanAmeringen M, Simon NM, Worthington JW, Hoge EA, Keshaviah A, Stein MB. A double-blind randomized controlled trail of augmentation and switch

strategies for refractory social anxiety disorder. *Am J Psychiatry*, 2014 Jan; 171(1):44-53. PMID 24399428

UPDATE ON NEUROMODULATION IN PSYCHIATRY: NIMH AND BRAIN INITIATIVE PRIORITIES*

Sarah Lisanby, NIH/NIMH

Individual Abstract: Neuromodulation is central part of modern clinical practice (e.g. transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT)), and new forms of neuromodulation are currently in development for the study and treatment of psychiatric disorders (e.g. transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), magnetic seizure therapy (MST), focused ultrasound (FUS) and others in development in the BRAIN Initiative). The basic mechanisms of how these interventions affect brain activity is an emerging science that will ultimately inform how to optimize and refine these techniques for clinical and research applications. This presentation will outline common challenges in optimizing dosage of neuromodulation for clinical efficacy, and highlight current funding priorities with NIMH and the NIH BRAIN Initiative relevant for neuromodulation.

Learning Objectives:

- Discuss state of the art of neuromodulation techniques currently approved in psychiatric treatment.
- Understand the key elements that define the dosage of neuromodulation.
- Discuss current priorities and funding opportunities for neuromodulation within NIMH and NIH BRAIN Initiative

Literature References:

- Radman T, Lisanby SH. New directions in the rational design of electrical and magnetic seizure therapies: individualized Low Amplitude Seizure Therapy (iLAST) and Magnetic Seizure Therapy (MST). *Int Rev Psychiatry*. 2017 Apr 21:1-16. doi: 10.1080/09540261.2017.1304898. [Epub ahead of print] PMID: 28430533
- Luber BM, Davis S, Bernhardt E, Neacsiu A, Kwapil L, Lisanby SH, Strauman TJ. Using neuroimaging to individualize TMS treatment for depression: Toward a new paradigm for imaging-guided intervention. *Neuroimage*. 2017 Mar 1;148:1-7. doi: 10.1016/j.neuroimage.2016.12.083. Epub 2017 Jan 3. PMID: 28062252
- Kellner CH, Husain MM, Knapp RG, McCall WV, Petrides G, Rudorfer MV, Young RC, Sampson S, McClintock SM, Mueller M, Prudic J, Greenberg RM, Weiner RD, Bailine SH, Rosenquist PB, Raza A, Kaliora S, Latoussakis V, Tobias KG, Briggs MC, Liebman LS, Geduldig ET, Teklehaimanot AA, Dooley M, Lisanby SH; CORE/PRIDE Work Group A Novel Strategy for Continuation ECT in Geriatric Depression: Phase 2 of the PRIDE Study. *Am J Psychiatry*. 2016 Nov 1;173(11):1110-1118. Epub 2016 Jul 15. PMID: 27418381
- Kellner CH, Husain MM, Knapp RG, McCall WV, Petrides G, Rudorfer MV, Young RC, Sampson S, McClintock SM, Mueller M, Prudic J, Greenberg RM, Weiner RD, Bailine SH, Rosenquist PB, Raza A, Kaliora S, Latoussakis V, Tobias KG, Briggs MC, Liebman LS, Geduldig ET, Teklehaimanot AA, Lisanby SH; CORE/PRIDE Work Group. Right Unilateral Ultrabrief Pulse ECT in Geriatric Depression: Phase 1 of the PRIDE Study. *Am J Psychiatry*. 2016 Nov 1;173(11):1101-1109. Epub 2016 Jul 15. PMID: 27418379

3:45 p.m. - 5:45 p.m.
Thursday Afternoon Workshops*

RAPID-ACTING ANTIDEPRESSANTS: PERSPECTIVE ON ISSUES IN NONCLINICAL AND CLINICAL DEVELOPMENT FROM THE DIVISION OF PSYCHIATRY PRODUCTS (DPP), FOOD AND DRUG ADMINISTRATION

Javier Muniz, US Food and Drug Administration

Overall Abstract: Currently marketed antidepressant drugs generally require several weeks of treatment before achieving therapeutic efficacy. This time course has shaped the clinical development programs for numerous antidepressants as well as influenced regulatory standards for marketing approval and post-marketing requirements.

In the past decade, there has been a renewed interest in the development of antidepressants with a shorter time to effect, in part due to studies suggesting that the N-methyl-D-aspartate (NMDA) channel blocker ketamine may reduce depressive symptoms within hours of administration. The development of antidepressants with novel mechanisms of action and quicker onsets of effect has been accompanied by evolving thought in the Division about regulatory issues related to the investigation and potential approval of these agents.

In this workshop, we will include presentations discussing the following topics:

1. Nonclinical requirement of rapid-acting antidepressants, with a focus on nonclinical safety concerns related to NMDA channel blockers
2. Study design of pivotal clinical trials, including selection and timing of the primary endpoint, assessments of treatment durability, and indication-related factors (e.g., monotherapy vs. adjunctive therapy, and standard vs. treatment-resistant depression)
3. Clinical trial assessments, interventions and procedures to enhance subject safety in the context of rapid acting antidepressants
4. Forthcoming updates to the FDA Guidance on the Assessment of Suicidal Ideation and Behavior, including the discussion of suicidal ideation and behavior as an endpoint and potential treatment indication
5. Other issues related to New Drug Application approval, including pediatric studies, postmarketing studies, and non-standard approval pathways

Learning Objectives:

- Be able to articulate the nonclinical data required by the FDA prior to human investigation of NMDA channel blocking antidepressants.
- Recognize important issues in drug development of a rapid-acting antidepressant.

RAPID-ACTING ANTIDEPRESSANTS: PERSPECTIVE ON ISSUES IN NON-CLINICAL AND CLINICAL DEVELOPMENT FROM THE DIVISION OF PSYCHIATRY PRODUCTS, FOOD AND DRUG ADMINISTRATION

Shiny Mathew, Center for Drug Evaluation and Research, US Food and Drug Administration

Individual Abstract: N-methyl D-aspartate (NMDA) receptor antagonists have been used for pain and analgesia for many decades. Recently, there has been an increased interest in the use of this class of drugs as rapid acting antidepressant for depression. Whereas the mainstream treatments such as tricyclic antidepressants, serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors take 6-8 weeks for alleviation of symptoms, during which time patients are at higher risk for suicide, a single dose of ketamine has been

known to show antidepressant effects within hours to days. In spite of its quick onset, the remission of depressive symptoms will likely require it to be used on a chronic intermittent basis or as adjunct therapy to other approved antidepressants.

NMDA receptor antagonists, in particular, channel blockers such as PCP, MK-801, ketamine, and memantine, are thought to cause two types of neuronal toxicities. In the young, developing brain, this drug class causes neuronal apoptosis, for which the evidence is now clear in both rodents and primates. In the adult rat brain, NMDA receptor antagonists are thought to cause neuronal degeneration and necrosis, stemming from excitotoxicity.

Neuronal degeneration is most commonly found in the retrosplenial and posterior cingulate cortices with increased severity in sexually mature female rats than in males. The U.S. Food and Drug Administration has been regulating NMDA channel blockers presuming that both types of neuronal toxicities translate to humans. Children under three years of age and pregnant and lactating women have been required to be either excluded or be adequately protected during clinical trials using NMDA channel blockers due to the finding of increased neuronal apoptosis. For testing NMDA channel blockers in adults, our current practice is to require pharmaceutical companies to conduct an acute single dose neurotoxicity study with their drug in sexually mature rats prior to phase I trials. Based on the results of this study, we limit Sponsors to 1/10th the NOAEL for the irreversible and unmonitorable toxicity of neuronal degeneration and necrosis. This talk will discuss the specific nonclinical regulatory requirements for clinical trials and marketing of NMDA channel blockers.

Learning Objectives:

- Participants will understand the spectrum of nonclinical toxicities caused by NMDA channel blocker administration.
- Participants will gain knowledge about the nonclinical regulatory requirements for clinical trials and marketing of NMDA channel blockers.

Literature References:

- De Olmos S, Bueno A, Bender C, Lorenzo A and de Olmos J. Sex differences and influence of gonadal hormones on MK-801 induced neuronal degeneration in the granular retrosplenial cortex of the rat. *Brain Struct Funct.* 2008 213:229-238.
- Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vockler J, Dikranian K, Tenkova TI, Stefovskaja V, Turski L, and Olney JW. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science.* 1999 283:70-74.
- Olney JW, Labruyere J and Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* 1989. 244:1360-2
- Slikker W, Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, Doerge DR, Scallet AC, Patterson TA, Hanig JP, Paule MG and Wang C. Ketamine induced neuronal cell death in the perinatal rhesus monkey. *Toxicol Sci* 2007 98:145-158.

RAPID-ACTING ANTIDEPRESSANTS: CLINICAL TRIAL DESIGN CONSIDERATIONS

Bernard Fischer, FDA/CDER/DPP

Individual Abstract: Conventional antidepressant drugs are typically administered orally each day and patients require 4 to 6 weeks of treatment before demonstrating significant improvement. Pharmaceutical companies have based their antidepressant development

programs on this paradigm. In order to minimize burden and maximize signal detection, subjects self-administer study drug for at least 6 to 8 weeks—only presenting to the investigator for study visits. This prototypical design is not appropriate for evaluating the new group of rapid-acting antidepressant drugs (RAADs). Most RAADs require non-oral administration, but produce a significant effect within hours that lasts for several days. This treatment model will influence the number and frequency of study visits. Additionally, the optimum clinical trial duration for RAADs is unclear. Previously, duration was based on catching the onset of effect. When the onset of effect is within hours, how long should subjects continue in a study? Other questions affecting trial design include: Will RAADs be used only acutely or also as chronic treatment? Will most use be adjunctive along with conventional antidepressants or as monotherapy? Should enrollment reflect only treatment-resistant depression or would RAADs be an acceptable choice for a new-onset, single-episode patient? This talk will discuss these issues in greater detail.

Learning Objectives:

- Participants will be able to discuss how time to clinical effect with conventional antidepressant drugs has shaped product development programs and how the current paradigm is challenged by rapid-acting antidepressants.
- Participants will be able to discuss how potential clinical use of rapid-acting antidepressants will influence clinical trial design.

Literature References:

- Katz MM. Need for a new paradigm for the clinical trials of antidepressants. *Neuropsychopharmacology*. 1998 Dec;19(6):517-22.
- Gelenberg AJ, Thase ME, Meyer RE, Goodwin FK, Katz MM, Kraemer HC, Potter WZ, Shelton RC, Fava M, Khan A, Trivedi MH, Ninan PT, Mann JJ, Bergeson S, Endicott J, Kocsis JH, Leon AC, Manji HK, Rosenbaum JF. The history and current state of antidepressant clinical trial design: A call to action for proof-of-concept studies. *J Clin Psychiatry*. 2008 OCT;69(10):1513-28.

RAPID-ACTING ANTIDEPRESSANTS: SELECTION AND TIMING OF EFFICACY ENDPOINTS

Michael Davis, US Food and Drug Administration

Individual Abstract: Antidepressants approved to date by the U.S. Food and Drug Administration, which are thought to function by modulating monoaminergic neurotransmission, generally require several weeks of treatment before achieving efficacy for Major Depressive Disorder. Efficacy has typically been demonstrated in the context of 6 to 8 week placebo-controlled trials, assessing the change from baseline to end of treatment on measures such as the Hamilton Depression Scale or the Montgomery-Asberg Depression Rating Scale. Recent studies of drugs with non-monoaminergic mechanisms of action, such as the N-methyl-D-aspartate (NMDA) channel blocker ketamine, have shown the potential for reducing depressive symptoms in hours. This significant difference in time to effect has generated questions of how to adequately demonstrate treatment efficacy. In this talk, issues related to efficacy endpoint selection and timing will be discussed. Specific topics will include the appropriateness of commonly-used depression rating scales in this context and the acceptability of primary endpoints occurring within hours to days after treatment. These perspectives from the Division of Psychiatry Products will be of potential interest to sponsors and investigators who are developing rapid-acting antidepressants for marketing approval.

Learning Objectives:

- Recognize potential limitations of using historical assessment measures for depression in the context of rapid-acting antidepressant development.
- Understand current thinking in the Division of Psychiatry Products, Food and Drug Administration, on providing clinical evidence of effectiveness for rapid-acting antidepressants.

Literature References:

- Ballard ED, Luckenbaugh DA, Richards EM, Walls TL, Brutsché NE, Ameli R, Niciu MJ, Voort JL, Zarate CA. Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. *Journal of psychiatric research*. 2015 Sep 30;68:68-73.
- Cusin C, Yang H, Yeung A, Fava M. Rating scales for depression. In *Handbook of clinical rating scales and assessment in psychiatry and mental health 2009* (pp. 7-35). Humana Press.

RAPID-ACTING ANTIDEPRESSANTS: CLINICAL TRIAL ASSESSMENTS, INTERVENTIONS AND PROCEDURES TO ENHANCE SUBJECT SAFETY

Andy Mattai, Center for Drug Evaluation and Research, US Food and Drug Administration

Individual Abstract: There are unique and differential safety concerns associated with the use of rapid acting antidepressants compared to traditional antidepressants. Using glutamatergic drugs as a prototype, I will discuss how collecting certain assessment measures can lead to an enhanced understanding of the safety profile of such medications. This will include a review of the appropriate scales to monitor manic, psychotic, and dissociative symptoms as well as suicidality. Due to the possible drug liking properties of many of these compounds, guidelines regarding the need for abuse liability studies will also be discussed. As participants in rapid acting antidepressant clinical trials may endorse varying degrees of suicidality and depressive symptoms, it is critical that appropriate safeguards be implemented to ensure subject safety from trial initiation to completion. These safeguards will be discussed in the context of addressing individual patient preferences, concurrent conditions, and maintaining appropriate standards of care. Lastly, I will discuss the regulatory considerations for the creation of the safety database and how this may impact the integrated analysis of safety.

Learning Objectives:

- Participants will gain familiarity with the safety concerns regarding the use of rapid acting antidepressants.
- Participants will gain knowledge about the regulatory considerations when establishing a safety database.

Literature References:

- Machado-Vieira R, Henter ID, Zarate CA Jr. New targets for rapid antidepressant action. *Prog Neurobiol*, 2015
- Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CA, Jr., Charney DS. Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. *Annu Rev Pharmacol*. 2014;54:119-139.

RAPID-ACTING ANTIDEPRESSANTS: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS

Jean Kim, FDA/CDER/DPP

Individual Abstract: Antidepressants approved to date by the U.S. Food and Drug Administration (FDA), which are thought to function by modulating monoaminergic neurotransmission, generally require several weeks of treatment before achieving efficacy for Major Depressive Disorder (MDD). Recent studies of drugs with non-monoaminergic mechanisms of action, such as the N-methyl-D-aspartate (NMDA) channel blocker ketamine, have shown the potential for reducing depressive symptoms in hours. This marked difference in time to effect for MDD has generated significant interest in programs for expedited development and review for these innovative drugs. In this talk, standard and non-traditional approaches (i.e., expedited programs) in drug development and approval will be discussed. Specific topics will include fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. Additional topics may include pediatric study requirements, expanded access (compassionate use), and postmarketing considerations. These perspectives from the Division of Psychiatry Products will be of potential interest to sponsors and investigators who are developing rapid-acting antidepressants for marketing approval.

Learning Objectives:

- Understand standard regulatory requirements and non-traditional approaches to drug approval for rapid-acting antidepressants.
- Recognize existing programs intended to help ensure that therapies for serious conditions are available to patients as soon as it can be concluded that the therapies' benefits justify their risks.

Literature References:

- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. (2014, May). Retrieved November 17, 2016, from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>
- Pediatric Product Development. (2016, October 11). Retrieved November 17, 2016, from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>
- Expanded Access to Investigational Drugs and Biologics. (2016, November 16). Retrieved November 17, 2016, from <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM502713.pdf>
- Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. (2012, August). Retrieved November 17, 2016, from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf>

HOW TO USE THE MODEL PSYCHOPHARMACOLOGY CURRICULUM IN VARIOUS TEACHINGS

Ira Glick, Stanford University School of Medicine

Overall Abstract: Started by the ACNP training committee in 1984, the ASCP Psychopharmacology Committee has developed unique and widely disseminated curricula for teaching clinical psychopharmacology to psychiatric residents, medical students and primary care physicians. It has increasingly had global penetration. We present here the 9th edition of

the resident curriculum, the 3rd edition for medical students and the 2nd edition for primary care. The ASCP Curriculum Committee composed of directors of both resident education as well as medical student education educators have developed materials related to the “what, why, and how” to teach and evaluate. In addition for each curriculum, we included both a core series of lectures as well as optional lectures developed by experts in their fields. We have done follow-ups on all three curriculums within the last 2 years. We describe here the process of revising, updating, and moving to a web-based curriculum. We present the content for the three curriculum. Based on the follow up of all three curriculum, we have revised every lecture and updated the pedagogy. Depending on the size/resources of the program, teachers use the curriculum in its entirety or in parts. It works even in non-English speaking countries as committee members work with users to adapt/translate to local conditions and teaching strategies. It has been difficult to connect with primary care training programs.

Learning Objectives:

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

PSYCHOTROPICS AND PREGNANCY: CURRENT PRACTICE TO EVIDENCE BASED APPROACHES*

Crystal Clark, Northwestern University

Overall Abstract: Pregnant women with affective disorders are at increased risk for mood worsening and episode recurrence during pregnancy. Too often, standard of care practices result in suboptimal management for the pregnant woman with mental illness due to 1) polypharmacy, 2) clinicians’ reticence to prescribe psychotropics during pregnancy, or 3) poor optimization of medication dose. This workshop will describe data on current practice and present available evidence to guide optimal psychotropic treatment in pregnant women. In the first presentation, Dr. Katherine L. Wisner will present data on the course of Bipolar Disorder (BD) and pharmacotherapy management in a sample of pregnant women treated in an urban community setting. Dr. Wisner’s presentation will highlight non-guideline concordant treatment approaches and its impact on wellness across pregnancy in women with BD. She will underscore the need for physician education and evidenced based guidelines to improve psychiatric outcomes. In the second presentation, Dr. Cara Angelotta will address next steps toward optimal treatment by providing an overview of the published literature on the risks and benefits of psychotropic use in utero versus untreated affective illness. Dr. Angelotta’s presentation will include a risk-benefit model that will provide a structure for clinicians to incorporate evolving reproductive outcome data. In the third presentation, Dr. Krista Huybrecht’s will discuss how to interpret drug safety data from large databases before making a choice on which medication to prescribe. In the final two presentations, Dr. Catherine Stika and Dr. Crystal Clark will present on factors that affect dosing of psychotropics across pregnancy. Dr. Stika will review the fundamental physiologic changes in pregnancy that increase clearance and, in many cases, decrease efficacy of pharmacotherapy, including psychotropics. Dr. Clark will present new data on the impact of pregnancy-related physiological changes on the pharmacokinetics of lamotrigine and lithium. Dr. Clark will describe how increased lamotrigine and lithium clearance across pregnancy impacts the course of BD. Finally, Dr. Matthew Rudorfer will serve as a discussant and will

integrate the key principles of each presentation to provide the audience with a clinical roadmap to optimizing psychotropic management in the pregnant woman with mental illness.

Learning Objectives:

- To identify key principles to guide risk/benefit assessment and management of psychotropics across pregnancy.
- To interpret evidence based information and apply it to the treatment of the pregnant woman with mental illness.

MOOD SYMPTOMS IN PREGNANT WOMEN WITH BIPOLAR DISORDER: HOW EFFECTIVE IS PSYCHOTROPIC TREATMENT?*

Katherine Wisner, Northwestern University Feinberg School of Medicine

Individual Abstract: Objective. To contribute information on the course of Bipolar Disorder (BD) and the impact of pharmacotherapy on women's mood symptoms across childbearing, we conducted an NIMH-funded prospective study of a community cohort of pregnant women with BD I, II or NOS. Our hypothesis was that psychotropic-treated women would have less symptom burden and functional impairment across childbearing compared to women not receiving pharmacotherapy.

Methods. We characterized symptoms of depression and mania throughout pregnancy and the first year after birth. The symptom levels of women who were not treated with psychotropic medications were compared. Assessments were scheduled at 20, 30, and 36 weeks gestation and 2 weeks and 3, 6.5 and 12 months postpartum. Symptoms were assessed with the Structured Interview Guide for the Hamilton Depression Rating Scale--Atypical Depression Supplement (SIGH-ADS) and Mania Rating Scale (MRS).

Results. Pregnant women (N=152) with BD participated. Eighty-eight women (58%) were treated and 64 untreated (42%) with psychotropic drugs during pregnancy. Among the 88 women treated, 23 (26%) discontinued their medication in the first trimester and the remainder were exposed throughout pregnancy or in Trimesters 2 and 3. Of the pregnant women treated with psychotropics, about half (n=50; 56.8%) received a guideline-concordant drug for BD: lithium alone/combination, n=7 (8.0%); anticonvulsant alone/combination, n=14 (15.9%); antipsychotic alone/combination, n= 29 (33.0%). Among the remaining 43.2% of the subjects, 12 (13.6%) received antidepressant monotherapy and the remainder (n=26, 29.5%) received mono- or poly-pharmacy with a variety of other agents including gabapentin, hydroxyzine, zolpidem, amphetamines, methylphenidate, atomoxetine, diphenhydramine, benzodiazepines, and buspirone. Following birth, the proportion of women treated with guideline concordant drugs remained at about half of those treated. More than two-thirds (n=78, 72.9%) of the women took psychotropics postpartum. The mean scores on the SIGH-ADS were in the mild range of depressive symptoms in both the psychotropic-treated and untreated groups in both pregnancy and postpartum. The majority of women had no or few symptoms of mania.

Conclusions. Explanations for non-guideline concordant drug treatment include reticence to prescribe antimanic drugs to pregnant woman and lack of experience treating perinatal women. Other non-drug treatment and behavioral approaches such as psychotherapy were recommended in preference to mood stabilizers for some participants in our study.

Pharmacotherapy of pregnant women with BD compels the use of drugs with demonstrated efficacy because reduction of disease burden is the justification for exposure of the maternal-

fetal pair. The treatment of childbearing women with BD deserves urgent clinical and research attention in parallel with physician education to improve psychiatric outcomes.

Learning Objectives:

- The risks and benefits of guideline-concordant medications for BD in pregnant and postpartum women.
- The course of symptoms of bipolar disorder across childbearing and the risks of depression, mania and postpartum psychosis.

Literature References:

- Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, Ramin S, Chaudron L, Lockwood C. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry*. 2009; 31(5):403-413.
- Wisner KL, Sit DK, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, Eng HF, Luther JF, Wisniewski SR, Costantino ML, Confer AL, Moses-Kolko EL, Famy CS, Hanusa BH.
- Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. *JAMA Psychiatry*, 2013;70(5): 490-498.

**RISK-BENEFIT ANALYSIS OF PSYCHOTROPIC USE IN PREGNANCY:
PRACTICAL GUIDELINES FOR CLINICIANS FROM A FORENSIC
PERSPECTIVE***

Cara Angelotta, Feinberg School of Medicine, Northwestern University

Individual Abstract: Background: Clinicians treating pregnant women with affective illness must make treatment recommendations despite less than ideal scientific information to guide them. Pregnant women are typically excluded from double-blind randomized controlled trials prior to psychotropic drug approval due to ethical and medico-legal concerns about the risk of drug exposure to the fetus. As a result, the available evidence on the risks of psychotropic medications during pregnancy are from case reports, case series, case-control, and retrospective and prospective cohort studies of varying quality and with conflicting findings. The confounding effects of mental illness, health behaviors, and socioeconomic factors associated with psychiatric disorders in pregnancy further complicate interpretation of the evidence. In this context, informed consent, medico-legal risk, and shared decision-making are practical concerns for clinicians treating pregnant women with affective illness.

Methods: We briefly summarize the published literature on the risks and benefits to the mother and fetus of psychotropic medication during pregnancy compared to the risks of untreated affective illness. We then review the elements of informed consent and how this relates to medico-legal risk in treating pregnant women with psychiatric illness. Finally, we present a risk-benefit model that provides a structure for clinicians to incorporate evolving reproductive outcome data.

Results: There is no “zero risk” solution in caring for the pregnant woman with affective illness: both the disorder and the medication present risks to the mother and the embryo-fetus. The risks of untreated or undertreated illness must be weighed against the risks (and potential benefits) of treatment options. For informed consent to be valid, the physician must disclose to the patient appropriate information regarding the risks, benefits, and treatment alternatives and the patient, given this information, must be able to express a voluntary choice. The physician tasked with conveying the risks and benefits of treatment options, as well as the

risks associated with untreated or under-treated illness, must also understand the patient's unique values, concerns, and life situation prior to proposing treatment options.

Significance: When women with affective illness plan a pregnancy or conceive, the clinician must assist them in deciding whether the benefit of continuing treatment for disease control outweighs the risk of the drug to the developing embryo-fetus. Many physicians are uncomfortable with drug treatment of pregnant women because of lack of expertise or concern about medico-legal liability. A review of the elements of informed consent and risk-benefit analysis to support decision-making for pregnant women with affective illness addresses a major clinical need.

Learning Objectives:

- Understand informed consent in decision-making for the treatment of pregnant women with affective illness.
- Provide a model of risk-benefit analysis to improve the care of pregnant women with affective illness and reduce clinician concerns about medico-legal risk.

Literature References:

- Wisner KL, Zarin DA, Holmboe ES, Appelbaum PS, Gelenberg AJ, Leonard HL, Frank E: Risk-benefit decision making for treatment of depression during pregnancy. *Am J Psychiatry* 2000; 157:1933-1940.
- Appelbaum PS, Gutheil TG: *Clinical Handbook of Psychiatry and the Law*, 4th Edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2007.

**NEW APPROACHES TO THE DESIGN AND ANALYSIS OF STUDIES
EVALUATING THE SAFETY OF PSYCHOTROPIC MEDICATIONS DURING
PREGNANCY***

Krista Huybrechts, Brigham and Women's Hospital, Harvard Medical School

Individual Abstract: Prescription medication use during pregnancy is common and increasing. It has been reported that 83% of publicly-insured pregnant women have a dispensing for one or more prescription medications, and 42% have a dispensing for a prescription medication classified in the former U.S. Food and Drug Administration categories D or X. Psychotropic medications are no exception. Yet, pregnant women are systematically excluded from pre-approval randomized trials that help FDA assess the safety of medications. Drug safety studies in pregnancy typically require very large study populations because the outcomes tend to be rare. Administrative healthcare databases are used increasingly for this purpose, but the strengths, weaknesses, and pitfalls of this approach are not well understood. One particularly relevant data source is the Medicaid Analytic eXtract (MAX) since Medicaid covers the medical expenses for 40-50% of births in the United States. The population includes a preponderance of young women, racial and ethnic minorities, and women with disabilities; all groups which are frequently underrepresented in clinical trials and voluntary cohort studies, but most at risk for adverse pregnancy outcomes. Moreover, psychiatric disorders are common in publicly insured populations. The key design and analytic issues to consider when using these data sources to evaluate drug safety in pregnancy will be discussed and illustrated using several recent and ongoing studies on the risk of adverse neonatal outcomes associated with in utero exposure to psychotropic medications (antidepressants, antipsychotics, stimulants, lithium) using the MAX data. These studies demonstrate the importance of distinguishing the effects of the medication from the effects of the (severity of the) underlying indication and the feasibility of doing so in the context of large healthcare databases. The opportunities that some of the newer

epidemiologic methods offer to pregnancy research related to psychotropic medications will also be presented. Whereas a broad variety of methods will be mentioned, the emphasis will be on sensitivity and robustness analyses. In particular, we will illustrate how sensitivity analyses and quantitative bias analyses can be used to test the strength of the findings under various assumptions in terms of exposure, outcome, and confounder misclassification; the use of positive and negative controls to evaluate the validity of the data source; and the use of external data to adjust for unmeasured confounders. We will end by presenting new initiatives on the value of pooling across multiple data sources to enable the evaluation of very rare exposures (e.g., polytherapy, dose) and to follow-up on safety signals generated in a single data source (stimulants, antipsychotics).

Learning Objectives:

- To provide an understanding of the strengths and weaknesses, and opportunities offered by large healthcare utilization databases to study the safety of psychotropic medications in pregnancy.
- To ensure participants gain knowledge and skills necessary to critically evaluate scientific evidence related to the safety of psychotropic medications in pregnancy.

Literature References:

- Huybrechts KF, Hernandez-Diaz S, Paterno E, Desai RJ, Mogun H, Dejene SZ, Cohen JM, Panchaud A, Cohen L, Bateman BT. Antipsychotic Medication Use in Pregnancy and Risk of Congenital Malformations. *JAMA Psychiatry* 2016;73(9):938-46.
- Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, Mogun H, Levin R, Kowal M, Setoguchi S, Hernandez-Diaz S. Antidepressant Use in Pregnancy and the Risk of Cardiac Defects. *The New England Journal of Medicine* 2014; 19;370(25):2397-407.

OBSTETRICAL PHYSIOLOGY AND ITS IMPACT ON PHARMACOKINETICS*

Catherine Stika, Feinberg School of Medicine, Northwestern University

Individual Abstract: Over the course of pregnancy, maternal physiology profoundly changes in ways that cause medications to be distributed, metabolized and cleared quite differently than in non-pregnant women. For many drugs, this may affect their concentrations so significantly that they are either too low to be effective or so high that they may produce unwanted maternal side effects or unexpected fetal toxicity. I will review those fundamental changes in maternal physiology that affect cardiac output, plasma volume, total body water and renal clearance and demonstrate the impact of these changes using several commonly prescribed medications. I will also show how the huge increases in the reproductive hormones, estradiol and progesterone, that occur in pregnancy, turn on a drug metabolizing system, called, the xenobiotic sensing system that originally developed to protect us from environmental chemicals that would otherwise overwhelm our reproductive system. This causes induction of hepatic metabolism that increases clearance of many other medications, including psychotropic medications.

Learning Objectives:

- To show how the changes in cardiac output, body water and renal function that occur in pregnancy impact pharmacokinetics of certain medications, requiring dosing modifications.
- To demonstrate how the changes in estrogen & progesterone concentrations that occur in pregnancy alter hepatic metabolism of many commonly used medications.

Literature References:

- Frederiksen MC, Stika CS: “Drug therapy in pregnant and nursing women”, in Principles of Clinical Pharmacology, 3rd edition, ed: Atkinson, Jr AJ, Academic Press, San Diego, CA, 2013.
- Avram MJ, Stika CS, Rasmussen-Torvik LJ, et al. Rationale and design for an investigation to optimize selective serotonin reuptake inhibitor treatment for pregnant women with depression. Clin Pharmacol Ther. 2016;100(1):31-3

PHARMACOKINETICS OF LAMOTRIGINE AND LITHIUM ACROSS PREGNANCY: EVIDENCE TO INFORM DOSE OPTIMIZATION

Crystal Clark, Northwestern University

Individual Abstract: Background: Pregnancy related physiological changes affect the elimination clearance of lamotrigine and lithium and has resultant effects on efficacy and toxicity in pregnant and postpartum women with Bipolar Disorder. Currently, guidelines to inform optimal dosing across pregnancy are urgently needed reduce the risk of BD episode recurrence.

Methods: Prospective longitudinal pharmacokinetic studies were conducted in thirteen women with BD who took lamotrigine (n=10) or lithium (n=3) across pregnancy. All participants were admitted to a clinical care research unit 2 to 3 times during their pregnancies and, when possible, at least once within 3 months postpartum. At each visit serial blood samples were obtained and mood symptoms were assessed with the Inventory of Depressive Symptomatology Self-Report (IDS-SR), the Generalized Anxiety Disorder (GAD-7) scale, Internal State Scale (ISS), and the Young Mania Rating Scale (YMRS).

Results: Elimination clearance of lamotrigine and lithium increased across pregnancy and lamotrigine half-life reduced by 50%. Preliminary data shows that elimination clearance of lamotrigine increased 103% ± 46% by 28 ± 5 weeks gestation and lithium elimination clearance increased 61% by 33 weeks gestation. Increased elimination clearance led to decreased plasma concentrations for both pharmacotherapies. Declining drug concentrations were correlated with increased dose requirements for lithium and lamotrigine during pregnancy but were not correlated with scores on the IDS-SR, ISS, YMRS, or GAD-7.

Conclusion: This novel investigation of lamotrigine and lithium pharmacokinetics across pregnancy in women with BD suggests that dose titration of lamotrigine and lithium may be required during pregnancy to maintain efficacy and accommodate for increased lamotrigine and lithium elimination clearance.

Learning Objectives:

- To describe changes in elimination clearance and plasma concentration of lamotrigine and lithium across pregnancy.
- To describe how to optimize dosing and monitor plasma concentrations of lamotrigine and lithium across pregnancy.

Literature References:

- Clark CT, Klein AM, Perel J, Helsel J, Wisner KL. Lamotrigine Dosing in Pregnant Patients with Bipolar Disorder. *Am J Psychiatry*, 2013 Nov 1;170(11):1240-7
- Viguera AC1, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, Zurick A, Cohen LS. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry*. 2007 Dec;164(12):1817-24

Friday, June 2, 2017

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

Friday Morning Panel Sessions

VALIDLY AND RELIABLY MEASURING FUNCTIONAL PERFORMANCE IN DEMENTIA PATIENTS ACROSS COUNTRIES AND LANGUAGES IN CLINICAL TRIALS

Magdalena Perez, inVentiv Health

Overall Abstract: Functional performance is one of the most important aspects to monitor in dementia, given that it impacts patient quality of life, helps determine the progression of the disease, and formulates care plans. For this reason, functional performance is often a co-primary outcome in Alzheimer's disease (AD) trials, though it is challenging to measure in global trials where activities and functional norms vary across cultures. Thus, how can global trials validly and reliably measure functional performance across sites, countries, and languages? This panel will explore this question by discussing the challenges in measuring functional performance globally, explaining the process of linguistically validating functional assessments across languages, and reviewing ways to train and monitor clinicians who administer functional scales. The Disability Assessment for Dementia (DAD), a validated functional assessment scale, will be used as an example to discuss these issues.

The first presentation will discuss the challenges of measuring functional performance with AD patients. As clinical trials have shifted toward treating earlier stages of AD, accurate measurement of functional performance has become increasingly important since it is highly indicative of a patient's dementia stage. This presentation will also review the properties that a dementia-related functional assessment should possess, including age-appropriate activities, activities affected by the disease process, and the ability to evaluate which activities are problematic and which aspects of performing the activity are impaired (i.e., initiating, executing, etc.). The DAD will be used to demonstrate some of these properties, while also commenting on the properties that the DAD fails to evaluate.

The second presentation will focus on linguistically validating functional assessments across languages and countries for clinical trials. Given that functionality closely mirrors patients' daily activities, translation of these scales require culturally sensitive adaptations, which must be minimal and selectively done to preserve the reliability and generalizability of clinical trial data across countries. Often country- and language- specific psychometrically validated scales, such as the Chinese DAD, undergo extensive modifications that no longer render it comparable to other data being collected in the trial. Cultural and semantic challenges as well

as involving the author of the scales during the linguistic validation process will also be discussed.

The last presentation will review ways to train and monitor clinicians from different countries who administer functional assessments in clinical trials. Ensuring that clinicians adhere to the standardize administration and scoring guidelines of functional assessments is challenging in global trials, since some scale items may be country-specific if cultural adaptations were made to the scale. Also, caregivers in some countries may find some questions overly intrusive (i.e., toileting), so clinicians may benefit from being trained on both the mechanics of administering the assessments and culturally sensitive ways to solicit the information. This presentation will also highlight common errors made by clinicians who were audio-recorded administering the DAD to subjects participating in a global AD trial.

Learning Objectives:

- Attendees will be able to describe the attributes that make valid and reliable functional assessment measures for use in demential trials.
- Attendees will be able to describe the linguistic validation process of translating functional assessments for use in clinical trials.

MEASURING FUNCTIONAL PERFORMANCE IN INDIVIDUALS ON THE DEMENTIA CONTINUUM: WHAT TO CONSIDER

Patricia Belchior, McGill University

Individual Abstract: Functional performance is usually defined in the literature as the ability to perform activities of daily living (ADLs). It includes basic ADLs, which are activities that we usually do automatically, such as eating or brushing teeth and instrumental ADLs (IADLs) which are more complex activities and usually crucial for independent living, such as managing finances or preparing meals. Many studies have compared ADL performance in normal aging, mild cognitive impairment (MCI) and dementia and it is well established that there is a continuum of ADL decline.

Research has demonstrated that individuals with dementia are experiencing increasing difficulties in performing their everyday tasks over the course of the disease and will eventually need assistance in the very basic ADLs. However, it is now established that these declines start much earlier in the disease process. In fact, individuals with MCI, although still independent in their ADLs and IADLs, are found to make more errors, take more time to complete tasks and be less efficient than normal older adults. This ADL decline usually has important consequences on the lives of these individuals and their family members.

Considering that ADL performance is one of the main diagnostic criteria to differentiate MCI and dementia, and in the absence of a cure or prevention strategies, we should have a better understanding of the nature of this decline so tailored interventions can be proposed earlier on with the hopes to improve quality of life. Specifically, measures of functional performance are recognized as being important for the diagnosis of dementia as well as for monitoring disease progression, evaluating the impact of intervention and determining the need for home assistance or institutionalization.

This presentation will provide an overview of the current state of the knowledge in measuring ADL performance in individuals on the dementia continuum. Emphasis will also be given to specific aspects to take into consideration in the evaluation process. The types of assessments used to measure performance in daily activities will be presented and the

strengths and limitations of the available instruments will be discussed. Additionally, the different domains and subdomains included in these instruments will be addressed as well as the role of executive functions (EF) on the performance of ADLs. Even though there is a focus on the impact of memory on performance, it is well established in the literature that EF plays a major role.

To help illustrate these important aspects, we will present the Disability Assessment for Dementia (DAD). Specifically, the DAD was developed to assess functional ability in four basic and ten instrumental activities of daily living (ADL) that are affected by the disease process and to help delineate areas of EF which may impair performance. The DAD has been translated in several languages and is currently used in clinical practice as well as an outcome measure in several international clinical trials. A shorter version of the measure, the DAD-6, developed to assess functional performance in individuals with MCI will also be discussed.

In conclusion, despite millions of dollars spent in the search for a cure, to date, there is not much that can be offered to patients after a dementia diagnosis. However, interventions still have the potential to improve overall function, quality of life and hopefully delay the disease onset. But, in order to provide tailored interventions for these individuals to improve their quality of life and reduce the caregiver burden, an accurate assessment of functional performance is crucial.

Learning Objectives:

- To understand the different aspects that should be considered in functional evaluations with individuals on the dementia continuum.
- To understand the strengths and limitations of different functional assessments.

Literature References:

- Gélinas, I., Gauthier, L., McIntyre, M., & Gauthier, S. (1999). Development of a functional measure for persons with Alzheimer's Disease: The Disability Assessment for Dementia. *American Journal of Occupational Therapy*, 53, 471-481.
- Belchior, P., Holmes, M., Bier, N., Mazer, B., Bottari, C., Robert, A., Kaur, N. (2015). Performance-based tools for assessing functional performance in individuals with mild cognitive impairment. *The Open Journal of Occupational Therapy*, 3, 1-21.

LINGUISTICALLY VALIDATING THE DISABILITY ASSESSMENT IN DEMENTIA (DAD) FOR USE IN INTERNATIONAL CLINICAL TRIALS

Christelle Giroudet, Mapi Language Services

Individual Abstract: Measures of functional performance like the Disability Assessment in Dementia (DAD) explore patients' activities of daily living: activities that one does in real life to cover basic needs are assessed to get information on how patients perform. These daily activities however generally reflect the cultural context of the region in which the measure was developed and are therefore culture-sensitive. When such a measure is to be used in the context of international clinical trials, there is a need to obtain translations that are faithful to the concepts of the original measure, linguistically appropriate and relevant to the cultural context of the countries they will be used in. Standard translation procedures does not permit to achieve these goals but linguistic validation does.

Linguistic validation is a rigorous and complex process specifically designed to preserve the properties of the source measure and allow pooling of data across countries. This process

includes several steps: conceptual definition, dual forward translations and reconciliation, backward translation, clinician's review and cognitive interviews. Each brings a different perspective and input into the translation. These steps will be described in detail in the presentation.

The DAD was linguistically validated into more than 60 languages, covering America (North, Central, South), Europe (Western, Scandinavia, Eastern also including Russia), South Africa, Asia and Oceania. Examples of challenges encountered during the linguistic validation of the DAD will be presented. From the "semantic" category of translation issues, two examples will be given. Example 1: Each task described in the DAD instrument fits into one category: "initiation", "planning and organization" or "effective performance." One difficulty in the translations consisted in finding the right verb(s) in the items that would match the stage of the act, particularly with the items in the "initiation" category. Translations of "undertake" were often a source of debate. Example 2: "Accidents" in the "Contingence" section had to be translated with a paraphrase in the languages where there is no direct equivalent to this idiomatic term. The last example that will be presented belongs to the "cultural" category of translation issues: "Choose appropriate utensils and seasonings when eating" from the Eating section. For the countries when one does not eat with utensils such as a fork and knife, this item had to be adapted to the cultural context while fitting in the category of "planning & organization." Critical elements in resolving translation difficulties will be discussed, such as the involvement of the author of the scale, Dr. Gelinas, as well as close interactions with the in-country participants in the linguistic validation process.

To conclude this part of the panel discussion, some practical considerations will be outlined, such as the need to use linguistically validated translations in clinical trials and to include a timeframe for linguistic validation in study planning if translations are not available.

Learning Objectives:

- Learn about the linguistic validation process for clinical outcome assessments.
- Learn about translation challenges with the Disability Assessment in Dementia (DAD).

Literature References:

- Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P, ISPOR Task Force for Translation and Cultural Adaptation. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR Task Force for translation and cultural adaptation. *Value Health* 2005; 8(2):94-104.
- Acquadro C, Conway K, Hareendran A, Aaronson N; European Regulatory Issues and Quality of Life Assessment (ERIQA) Group. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. *Value Health* 2008; 11(3):509-21.

TRAINING AND MONITORING CLINICIANS ADMINISTERING FUNCTIONAL ASSESSMENTS IN DEMENTIA GLOBAL TRIALS

Magdalena Perez, inVentiv Health

Individual Abstract: Introduction: Obtaining a valid and reliable measure of functional performance in global Alzheimer's disease (AD) trials can be challenging. Unlike other outcome measures collected in AD trials (i.e., measurements of cognition), functional

performance is highly influenced by the societal and cultural background of patients (Mok et al., 2005). For this reason, the items evaluated within a functional assessment may vary across countries, which may compromise the quality of the data collected. This discussion focuses on methods to ensure valid and reliable data are collected on functional assessments by providing standardized culturally sensitive scale training to clinicians administering these scales and by monitoring their administration of these scales.

Methods: To facilitate discussion, two sets of data will be presented. First, data will be presented to describe a culturally sensitive training program on a functional assessment scale, the Disability Assessment for Dementia (DAD; Gelinas et al., 1999), which was provided to 240 clinicians participating in two global AD trials from the United States, Japan, South Korea, Czech Republic, Italy, Poland, and South Africa. These clinicians completed a one-hour didactic session on the DAD guidelines, followed by the completion of a culturally neutral evaluation exercise where they rated a written vignette illustrating the caregiver responses to the DAD items. The inter-rater reliability (IRR) of clinicians' performance on the vignette will be presented to illustrate the efficacy of the training program. Second, data will be presented on how clinicians performed on their first in-study administration of the DAD. The clinicians were asked to audio-record their first in-study administration of the DAD and submit it for review by a cultural expert from their respective countries. A total of 133 audio-recorded administrations were reviewed and rated on Rating Adherence (RA_d) and Rating Accuracy (RA_c). Clinicians' performance on their in-study DAD administrations will be presented to illustrate challenges across countries.

Results: Preliminary analyses conducted on the first set of data examining the efficacy of the training program indicated that Gwet's AC1 index of IRR agreement for the DAD item scores range from Fair to Perfect agreement across the group of clinicians. There were only three out of the 40 items evaluated that had Fair agreement. Preliminary analyses conducted on the second set of data examining clinicians' performance on their first in-study DAD administration indicated that the clinicians on average obtained lower scores on RA_c than RA_d. Minor country differences were also detected.

Conclusion: The panel will discuss aspects of the training program that led to overall strong degrees of IRR on the DAD exercise, although the clinicians were from different countries. The importance of including a culturally neutral exercise helped established consensus amongst the clinicians on the majority of the items, and also pointed out items that were most likely to differ across countries. As the clinicians moved onto administer the DAD to patients participating in the trial, clinicians were able to maintain a strong degree of adherence to the administration guidelines, but seemed to struggle in accurately rating the information that was being obtained. The panel will discuss the importance of integrating culturally sensitive trainings into global trials, and propose methods to decrease rating inaccuracies on functional assessments.

Learning Objectives:

- Attendees will be able to describe the importance of culturally sensitive scale trainings in global trials.
- Attendees will learn ways to effectively monitor functional assessment data being collected from different countries.

Literature References:

- Gelinas, I., Gauthier, L., McIntyre, M., & Gauthier, S. (1999). Development of functional measure for persons with Alzheimer's disease: The Disability Assessment for Dementia. *The American Journal of Occupational Therapy*, 53, 471-481.
- Mok, C.C.M., Siu, A.M.H, Chan, W.C., Yeung, K.M., & Pan, P.C. (2005). Functional disabilities profile of Chinese elderly people with Alzheimer's disease—A validation study on the Chinese version of the Disability Assessment for Dementia. *Dementia Geriatric Cognitive Disorders*, 20, 112-119.

SUICIDAL BEHAVIOR IN THE CLINICAL SETTING: RELATIONSHIP BETWEEN ADHD, DEPRESSION, AND DECISION-MAKING CAPACITY*

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Overall Abstract: Depression and suicide are among the leading causes of global disability and death. Research has demonstrated that adolescents with a history of attention deficit hyperactivity disorder (ADHD) are significantly more likely to develop comorbid conditions including depression, anxiety, and substance use by early adulthood. Moreover, ADHD and depression are heritable disorders that share genetic etiological risk factors including altered reward and decision-making processing. Blunted response to reward, anhedonia, and impaired cost-benefit decision-making are present in ADHD and depression and have been postulated to be responsible for the increased risk of maladaptive emotional-based coping, risk-taking behavior, and self harm. Moreover, there is growing evidence that ADHD symptom severity and chronic anhedonia are positively correlated with the development of treatment resistant depression and risk of suicidality.

Over the past few decades there has been a growing body of evidence that supports ADHD as a risk factor for premature death due to accidents and risk-taking behaviors. Although a family history of psychiatric illness and suicide, a personal history of physical and/or sexual abuse, and a recent personal loss have been widely accepted as important risk factors for suicidal behaviors, studies have demonstrated that the presence of ADHD plays an important role in the development of self-harm and suicidal behaviors in adulthood. In fact, several studies have reported an increased risk of suicidal ideation as well as attempts and completed suicide in individuals diagnosed with ADHD. Despite initial evidence that suggested that ADHD exacerbated the effects of other psychiatric illness such as depression, more recent research has demonstrated that a strong correlation between ADHD symptoms and attempted and completed suicide independent of psychiatric comorbidity.

This presentation will review the epidemiology of co-occurring ADHD and depression as well as the implications of blunted reward and decision-making capacity on the manifestations and risk of suicidal behavior including ideation and attempt. The neurobiology of emotional dysregulation, anhedonia, and decision-making capacity in relation to suicidal behavior with a focus on biological dysfunctions present in co-occurring ADHD and depression will be discussed. The panel will focus on the use of clinical features and a novel approach to understanding and identify those at risk of poor response to antidepressant therapy and increased risk of suicidal symptoms.

Learning Objectives:

- To recognize the prevalence and impact of co-occurring ADHD and depression on the manifestation of self-harm and suicidal behavior.
- To identify the neurobiological links between ADHD and depression that may predict symptom severity and suicidal behaviors.

PHENOTYPES OF SUICIDALITY IN DEPRESSED PATIENTS*

Irvin Epstein, University of Toronto

Individual Abstract: There have been major advances in our understanding of the link between chronic suicidality and genetic predisposition, with recent research focusing on understanding the relationship between genotypes and phenotypes of suicide. There is a strong positive correlation in families of individuals who have a history of completed suicide and increased incidence of subsequent attempts and completions in first-degree offspring in the order of 4-7 times across studies. Research indicates that both depressive disorders and suicidal ideation in offspring correlate with having a depressed parent, which increases based on severity of the parent's diagnosis. Suicidal behavior of the offspring on the other hand, does not seem to be correlated or affected when rates of psychiatric disorders were controlled for. Thus, it appears that suicidal behavior functions independently from the severity of a psychiatric diagnosis in offspring.

Evidence from studies focusing on the neurobiological underpinnings of suicidal ideation and/or behaviors suggest that their presence is the result of a number of unique and heritable genetic factors, often similar to those of most other psychiatric disorders, including dysregulation of neurotransmitters. Our current understanding of the importance of biomarkers such as definitive genetic properties and associated vulnerabilities of suicidal patients, has established that genes associated with the serotonergic system including the higher serotonin 1A binding potential of the raphe nuclei are strongly implicated in the evolution/generation of both suicidal behavior and ideation. When these underlying vulnerability factors occur in the presence of multiple environmental stressors, it increases the rate of severe attempts by 55%.

The rationale for increased attention is motivated by a desire to reduce the devastating mortality and impact on families and society at large. Advances improve our clinical knowledge and help to improve our resources towards better and earlier diagnosis and targeted treatment options, to improve best practice methods of care. The link between affective disorders and suicidal behavior will be investigated in terms of recent literature regarding genetics. The presenter will also review the evidence of unique sub-phenotypes of suicidal behavior associated with levels of dysregulation of an individual's serotonergic system. Finally, the presenter will examine the genetic mechanisms and biochemical phenotypes associated with overt suicidal ideation and behavior in a clinical population.

Learning Objectives:

- To recognize variation in genetic risk factors associated with suicidal ideation and attempt.
- To gain an understanding of the impact of alterations in the serotonergic system in the development and expression of suicidal behavior and ideation.

Literature References:

- Brent D. What family studies teach us about suicidal behavior: implications for research, treatment, and prevention. *European Psychiatry*. 2010 Jun 30;25(5):260-3.
- Courtet P, Jollant F, Castelnau D, Buresi C, Malafosse A. Suicidal Behavior: Relationship between phenotype and serotonergic genotype. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 2005 Feb 15;133(1):25-33.

CHRONIC ANHEDONIA: A RISK FACTOR FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER AND SUICIDAL BEHAVIOR IN DEPRESSED ADULTS*

Tia Sternat, START Clinic for Mood and Anxiety Disorders

Individual Abstract: Depression and suicide have become a major public health concern as rates continue to increase and have become among the leading causes of disability and death respectively. Research suggests that more than 11% of adolescents experience depression and that depressed adolescents are 6-times more likely to attempt suicide compared to non-depressed individuals. As well, adolescents with a history of attention deficit hyperactivity disorder (ADHD) are significantly more likely to develop depression and self-harm behavior by early adulthood. A core symptom of depression, anhedonia, is present in a subset of patients with ADHD and associated with poorer treatment response in patients treated with traditional antidepressants.

In general the capacity to experience pleasure derived from everyday activities varies from person to person. Individuals with low hedonic tone perceive daily activities as less pleasurable and require more stimuli to raise their baseline hedonic tone. Without the presence of this stimulation, individuals with low hedonic tone are prone to chronic low mood, risk-taking behavior, and executive dysfunction, commonly present in ADHD. Historically reward-related research has focused on mesolimbic dopaminergic system, advances in neuroscience have provided evidence that suggests that hedonic tone is modulated by multiple systems, each responsible for specific reward processing-related activities. Hence, gaining an understanding of the neurobiological pathways related to symptomatic presentation may lead to further insight into the vulnerability and variation in suicidal behaviors.

This presentation will focus on recent findings that demonstrated that the presence of chronic anhedonia or low hedonic tone may be a link between TRD and ADHD, which may predict poorer treatment outcomes and increase the risk of suicidality in a subset of patients treated with SSRIs. As well as highlight a novel approach to identify maladaptive coping styles and processes and diagnosis of comorbid psychiatric conditions.

Learning Objectives:

- To describe the direct and indirect pathways to self-harm common in individuals with co-occurring ADHD and depression.
- To identify behavioral and clinical features that may predict treatment outcome and suicidal behaviors in a subset of depressed patients treated with SSRIs.

Literature References:

- Taylor MR, Boden JM, Rucklidge JJ. The relationship between ADHD symptomatology and self-harm, suicidal ideation, and suicidal behaviours in adults: a pilot study. *ADHD Attention Deficit and Hyperactivity Disorders*. 2014 Dec 1;6(4):303-12
- Van Eck K, Ballard E, Hart S, Newcomer A, Musci R, Flory K. ADHD and Suicidal Ideation The Roles of Emotion Regulation and Depressive Symptoms Among College Students. *Journal of Attention Disorders*. 2015 Aug 1;19(8):703-14.

NEUROBIOLOGICAL VARIANCE IN SUICIDE ATTEMPT AND IDEATION: CLINICAL AND TREATMENT IMPLICATIONS*

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Individual Abstract: As rates continue to rise steadily, suicide has become a global public health concern. Given the heterogeneous nature, complexity of risk factors, and the high prevalence of comorbid psychiatric conditions associated with suicidal behavior, there has been an increased interest in identifying the biological basis of suicidality in an effort to uncover risk factors that predispose or predict individuals to a higher risk of attempt and/or ideation and identify specific phenotypic presentation. Research has suggested that although attempts and completed suicides may share a common genetic basis, suicidal ideation may not be linked genetically to either suicidal attempts or chronic self-harm behaviors. Furthermore, suicidal ideation appears to differ in heritability compared to attempts and violent self-harm behavior, which may be due to a combination of factors including neurobiological variation in reward and decision-making capacity.

This presentation will focus on genes implicated in the suicidal phenotypes, such as those involved in the serotonin system, including TPH1 and TPH2, the serotonin transporter 5-HTTLPR, and MAOA levels. Furthermore, neurobiological pathways common to depression, ADHD, and suicidal ideation will be discussed. The presenter will highlight the impact of childhood adversity in relation to suicidal risk, as well as implications of age of onset of depression and suicidal behavior, in order to assess suicidal risk across the lifespan. As well, implications of intergenerational trauma and its impact on familial transmission of suicidal behavior will be discussed. In this section, the neuroanatomy and neurobiology suicidality will be reviewed and recent data from neuropsychology and genetics associated with suicidal attempt and ideation will be presented, highlighting the common links and differences between the subtypes. Further, treatment interventions that target of individuals at risk of suicidal behavior or ideation will be presented and discussed in relation to long-term outcomes.

Learning Objectives:

- To provide an understanding of specific neural circuits and catecholaminergic dysregulation implicated in suicidal ideation and attempts.
- To explore clinical presentations that may predict treatment outcome and guide treatment selection.

Literature References:

- Beblo T, Sinnamon G, Baune BT. Specifying the neuropsychology of affective disorders: clinical, demographic and neurobiological factors. *Neuropsychology review*. 2011 Dec 1;21(4):337-59.
- Turecki G. The molecular bases of the suicidal brain. *Nature Reviews Neuroscience*. 2014 Dec 1;15(12):802-16.

NEW TECHNOLOGIES FOR REDUCING PLACEBO RESPONSE AND IMPROVING SIGNAL DETECTION IN CNS CLINICAL TRIALS

Michael Detke, Indiana University School of Medicine

Overall Abstract: Only 8% of CNS drugs that enter clinical studies eventually receive approval - lower than almost all other therapeutic areas. 50% & 22% of clinical trials of FDA-approved antidepressants and antipsychotics, respectively, fail to demonstrate

superiority to placebo, and the placebo response has been increasing over time (Khin, 2011; Khin 2012). Pooled industry data show that efficacy in phase II studies is the most crucial step (Paul, 2010). These studies determine whether novel targets for psychiatric disorders are clinically validated. Failures here have slowed our understanding of the pathophysiology of these disorders and have discouraged further research in Neuropsychopharmacology.

Dr. Rabinowitz will present data on the frequency of patients enrolling in more than one clinical trial, often for the same disease, at the same time. This is validated with an analysis of the NewMeds integrated database of patient level data from 40 placebo controlled RCT's of antidepressant drugs and 29 RCT's of antipsychotic drugs. He will also present data on how this problem can be mitigated with patient registries.

Dr. Sachs will present data showing higher placebo response among subjects randomized with low confidence on eligibility criteria, diagnostic validity, and rating scale scores. The data suggest using quality metrics as eligibility criteria may improve signal detection. He will also present data on tandem rating of key efficacy measures, demonstrating in multiple randomized controlled trials that this may reduce placebo response and improve signal detection.

Dr. DeSommer will review data showing that that single stage randomized double-blind controlled designs result in an unsustainable rate of negative or failed trials. He will go on to present data supporting the conclusion that trial designs with two randomized double-blind placebo-controlled stages, such as the sequential parallel comparison design (SPCD) and the two-way enriched design (TED) proactively and effectively address high placebo response and variability.

Dr. Detke will discuss data on how therapeutic alliance, expectation bias and increased variance can increase the risk of trial failure. Several options for improving clinical trial outcomes and signal detection will be reviewed, along with recent data on each from several randomized controlled CNS clinical trials.

Learning Objectives:

- The attendees will learn about the challenges of increasing placebo response and decreasing drug-placebo signal detection in CNS clinical trials.
- The attendees will learn about new technologies to address the above challenges, and increase their understanding of the applicability of these new technologies.

NEWMEDS DATA ON DUPLICATE AND SEQUENTIAL ENROLLMENT IN CLINICAL TRIALS AND ONLINE REGISTRY TO REDUCE DUPLICATE AND SEQUENTIAL ENROLLMENT

Jonathan Rabinowitz, Bar-Ilan University

Individual Abstract: Background: There is emerging evidence, and growing concern, that subjects simultaneously and consecutively enroll in clinical trials, a practice that can lead to false or negative studies and has led to death and serious adverse events. As part of the Innovative Medicines Initiative sponsored NEWMEDS project, one of the largest ever-international academic-industry research collaborations aimed at improving the efficiency of clinical trials in schizophrenia and depression, we examined the extent to which subjects dual enroll in studies of antipsychotic and anti-depressant medications, motivations of persons who enroll concurrently in more than one clinical trial and developed a cross sponsor precompetitive data sharing online global registry to help prevent duplicate enrollment across trials and indications.

Methods: Data was from NEWMEDS repository of patient level data on 34,237 subjects from 96 clinical trials in schizophrenia and depression. Apparent duplicate enrollment by region was examined by matching subjects on available demographic information. For two studies, data were re-analyzed after removing duplicate subjects to examine their impact on efficacy results. In addition, we did 20 in-depth interviews, using opportunity sampling, with study participants, study personnel and study monitors to understand why persons duplicately enroll.

Results: The results of the analysis of duplicate and sequential enrollment showed apparent duplicates by region as follows: North America, 8.6%, Western Europe 4.8%, India 14.1%, Eastern Europe, 6.5%, Australia 7.8%. Also examined was data from all seven studies from one drug development program that showed that duplicates per study ranged from 11% to 14.8%. Data from one antidepressant study and one antipsychotic study suggest that even as few as 5% of subjects is sufficient to change study results from being statistically significant to being non-significant. Based on the interviews, the reasons for duplicate enrollment were categorized into the following main categories: (1) I know better, it is a silly requirement; (2) Investigational drug, not me I am not a criminal; (3) I am on a study for a cream, this is a study for a pill; it is not the same. They don't mean me; (4) They miscalculate, previous study ended 100 days ago; (5) They don't understand the question and are embarrassed to ask; (6) They want to be paid for an additional study; and (7) They, or their accompanying family member, are desperate and want to increase the chances of getting active treatment.

Conclusions: The data provides some minimum estimate of duplicate enrollment, as we did not have data on the entire universe of clinical trials. However, we could not estimate false positives. Results suggest that like many trials, these trials included duplicate patients. Having data on additional variables would have reduced the chance of false positives. The interviews suggest that there is a broad range of reasons for duplicate enrollment running the gamut of outright fraud to the desire to get needed treatment. Duplicate enrollment can be minimized by using a global clinical trial participant registry such as the NEWMEDS DupCheck tool, which can be used to screen out duplicate patients before enrollment. It uses either data manually entered into system or data automatically streamed via EDC/IVR/IRT. System can also be used to re-analyze completed trials after removing duplicate patients.

Learning Objectives:

- Understand the extent to which duplicate and sequential enrollment can harm clinical trials. Gain insights on why subjects duplicately enroll.

Literature References:

- Resnik DB, McCann DJ. Deception by Research Participants. *N Engl J Med.* 2015;373:1192-1193.

LEARNING FROM A COMPUTER SIMULATED RATER: LESSONS IN SIGNAL DETECTION

Gary Sachs, Bracket

Individual Abstract: Background: Inconsistency in signal detection, the ability of randomized controlled trials to find significant drug-placebo differences, is frequently cited as a cause of disinvestment in CNS drug development. Key determinants of clinical trial success are accession of a sample meeting eligibility criteria, reliable outcome assessment, and mitigating placebo response. Attempts to design protocols to achieve better performance across these domains have produced ever more complex studies and a proliferation of

programs for rater training, surveillance, and remediation. These efforts have produced higher costs, increased respondent burden, and much frustration, but results remain inconsistent.

Computer simulated raters (CSR) can administer legacy outcome measures (e.g. MADRS) as well as collect routine patient reported outcomes. Over the past decade computer simulated raters have been employed in randomized clinical trial for several purposes: quality control, independent assessment of eligibility, secondary outcome measure, and as a primary outcome measure.

Methods: This presentation reviews clinical trial data comparing measures obtained by a CSR with those obtained by site based raters (SBR). Most CSR trials have used a tandem rating design in which the SBR and CSR conduct assessments independently at the same study visit. Unlike self report scales, the CSR uses algorithms to mimic the judgment of a SBR administering a structured assessment (e.g. HAM-D or YMRS).

Results: **Eligibility:** SBR detected no drug-placebo difference for either of two doses of an FDA approved antimanic agents (N=504). The CSR found only 201 (39.9%) met criteria for acute mania before randomization, but in this subset the effect size favoring active drug was 2-5 x greater than that observed in the 303 subjects for which the CSR did not confirm eligibility. During an MDD study the mean ICC shows a slight dip from screen (.57) to baseline (.53) and remained above .72 for all post randomization visits. The ICC for most SBRs at high enrolling sites reveals more pronounced drops >0.3 and tend to follow a more erratic pattern after randomization. **Outcome Reliability and placebo response:** In a bipolar depression study, slightly better effect sizes were found by the CSR compared to the SBR, but both rating systems showed subjects with high discordance (absolute value SBR-CRS) at baseline, had better response to placebo than to active drug with large effect sizes. Similarly, in a successful phase III study for MDD the drug placebo difference was approximately double in the subset with concordant SBR-CRS scores at baseline. Among subsets discordant at baseline moderate-large effect sizes favoring placebo were observed.

Conclusion: Use of Tandem ratings in which one of the ratings is a CSR can enhance signal detection when incorporated into protocol specified eligibility criteria, but has less impact when used solely as a quality metric. Large discordance between SBR and CSR at baseline are associated with large placebo response. Overall signal detection based on outcome measures administered by a CSR are similar to those obtained by well-trained SBRs.

Learning Objectives:

- Participants will understand advantage of a tandem rating strategy to overcome the problem of low kappa for DSM diagnoses.
- Participants will recognize the potential to limit placebo response by using parameters associated with rating discordance as an eligibility criterion.

Literature References:

- Reilly-Harrington NA, DeBonis D, Leon AC, Silva L, Perlis R, Lewis D, Sachs GS. The Interactive Computer Interview for Mania. *Bipolar Disord.* 2010 Aug;12(5):521-7.
- Sachs GS, Vanderburg D, Edman S, Karayal ON, Kolluri S, Bachinsky M, Cavus I: Adjunctive Oral Ziprasidone in Patients With Acute Mania Treated With Lithium or

**CLINICAL TRIAL DESIGN, CONDUCT AND ANALYSIS METHODOLOGY
OPTIONS TO REDUCE RISK, TIME, COST, AND ENABLE SIGNAL DETECTION
IN THE PRESENCE OF HIGH PLACEBO RESPONSE AND VARIABILITY IN
NEUROSCIENCE**

Marc De Somer, PPD

Individual Abstract: The purpose of the randomized controlled clinical trial (RCT) is to provide valid, reliable, robust evidence to predict the optimal administration parameters and the corresponding benefit-risk of a therapeutic intervention. Individual patients and health care providers (HCPs) use this evidence to make therapeutic decisions, based on the assumption that the patient intends to take a complete treatment course as prescribed. In addition, RCT evidence is used by public health and regulatory authorities for community-level policy-making, accounting for real-world variability in completion, adherence and other covariates.

Powerful forces, associated with high and rising placebo response and heterogeneity, undermine therapeutic signal detection in contemporary clinical trials, especially in psychiatry. Clinical trials represent a selected sample of patients with a mixture of primary illness and co-morbidity patterns, varying adherence, retention and co-interventions.

Changes in patient and investigator behavior, expectations, perceptions, observation and reporting also affect trial outcomes.

Our review shows that single stage randomized double-blind controlled designs result in an unsustainable rate of negative or failed trials. This includes trials with an open-label, single- or double-blind lead-in period. Placebo or active lead-in designs have not resulted in improved therapeutic signal detection.

Trial designs with two randomized double-blind placebo-controlled stages, such as the sequential parallel comparison design (SPCD) and the two-way enriched design (TED) proactively and effectively address high placebo response and variability.

The first randomized double-blind placebo-controlled stage of SPCD enables the identification of genuine placebo nonresponders. These are re-randomized to active and placebo in SPCD stage 2. The SPCD analysis accounts for all stage 1 data and stage 2 placebo nonresponders.

TED is a variant of SPCD, adding the identification of genuine active responders in a randomized double-blind placebo-controlled first stage, followed by a rerandomization of active responders and placebo nonresponders in stage 2. TED trials enable the identification of target patients, and the accurate assessment of therapeutic response among active responders.

We compare operating characteristics of statistical models and missing data handling methods for continuous and binary endpoints in single- and two stage designs. Our empirical and simulation evidence highlight the integrity, efficiency, validity and reliability of SPCD and TED. Simulations were conducted across a wide range of assumptions, including treatment response, missing data rates and patterns, statistical analysis models and missing data handling methods. Robust type I error control, significant gains in power versus sample size, accuracy and precision are demonstrated.

Additional measures are helpful to ensure the validity and reliability of clinical trial evidence, including verification of patient eligibility, continuous patient engagement, monitoring and promotion of adherence, retention and data quality. Real-time data acquisition and data review enable timely correction or remediation.

We have identified and defined valid and reliable design, conduct, analysis and reporting options, that effectively reduce risk, time and cost of clinical trials in the presence of high placebo response and variability. Upfront demonstration of their integrity, transparency, validity, reliability, efficiency and robustness are essential to inform optimal sponsor decisions and effective regulatory interactions.

Learning Objectives:

- To examine the design, conduct, analysis and reporting of the randomized double-blind controlled clinical trial (RCT) from different stakeholder's viewpoints, and understand the distinction between RCT evidence relevant for individual patient-prescriber therapeutic decisions or for community-wide public health, payer and regulatory policy-making. To propose a novel standard for the reporting of clinical trial findings, to account for the high placebo response and heterogeneity, and enable transparency in the presentation of RCT results among different categories of patients, including completers and noncompleters, adherers and nonadherers, active- and placebo responders and nonresponders.
- To evaluate the rationale, strengths and limitations of conventional single-stage versus two-stage RCTs in the context of today's clinical trial ecosystem, with high placebo response and significant heterogeneity among patients, investigators, outcomes and measurements. To propose a novel framework for optimal trial design decisions as well as transparency in the reporting of trial results, in particular for two-stage trials.

Literature References:

- Chen YF, Yang Y, Hung HMJ. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. *Contemp ClinTrials*. 2011; 32(4): 592-604.
- Fava M, Evins AE, Dorer DJ, Schoenfeld DA. The problem of the placebo response in clinical studies for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003; 72(3): 115-27.
- Ivanova A, Tamura RN. A two-way enriched clinical trial design: combining advantages of placebo lead-in and randomized withdrawal. *Stat Methods Med Res*. 2015; 24(6): 871-90.
- Khin NA, Chen YF, Yang Y. Exploratory analyses of efficacy data from major depressive disorder studies submitted to the US Food and Drug Administration in support of new drug applications. *J Clin Psychiatry*. 2011; 72(4): 464-72.
- Khin NA, Chen YF, Yang Y. 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; 73(6): 856-64.

EXPECTATION BIAS AND VARIANCE: CHALLENGES TO CNS TRIAL SIGNAL DETECTION AND SOME NEW TECHNOLOGIES TO MINIMIZE THEM

Michael Detke, Indiana University School of Medicine

Individual Abstract: Background: Expectation bias and error variance are of particular concern in CNS trials due to the subjective nature of many outcomes. Rater expectation bias

may occur when raters expect that subjects will improve over the course of the trial. Subject expectation bias may occur when subjects themselves expect to get better. Finally, in traditional trial designs, rater and subject expectations may interact to create an alliance, resulting in increased placebo response and possibly decreased drug-placebo separation.

Error variance can be increased with subjective endpoints in many ways: increased numbers of sites/raters, non-adherence to scale methodologies such as structured interview guides (SIGs) and subtle differences in language, culture and medical practice across geographies.

Methods: I will review data on rater and subject expectation bias across multiple disease areas to illustrate the impact of expectation bias on placebo response and signal detection, and I will examine the design of these studies to identify methods for potentially mitigating expectation bias. I will also review the impact of increased variance on reducing signal detection (statistical power) and some recent data on the sources of variance.

I will then present data from CNS trials in anxiety and Parkinson's psychosis to examine the impact of these methods on signal detection (e.g., blinding to study visit number). In a study of GAD, placebo-treated subjects were assessed by both face-to-face raters (FFR) and blinded independent (BIR) raters on the Hamilton Anxiety Scale. A study of psychosis in Parkinson's disease included FFR at sites outside the US, and BIR on patients in the US. Use of BIR requires the application of technologies such as video- and tele-conferencing.

I will also present data from recent studies of depression and schizophrenia in which FFR were supplied with tablet-based software to assess for inconsistencies in scoring and to encourage use of SIGs and mitigate other sources of variance.

Results: Expectation bias is seen across several disease states, in subjects and raters, and can increase placebo response and decrease signal detection. Blinding raters to study visit mitigates expectation of improvement as treatment progresses. Using different raters across visits reduces the likelihood of relationship bias between rater and subject that could influence ratings. Recent studies showed reduced placebo response and/or increased signal detection using different BIR at consecutive visits.

Likewise, (error) variance is common across disease states in which subjective outcome measures are used. Two recent studies show that tablet-based software revealed many inconsistencies in scoring (likely increasing error variance). 40-73% of raters would have been alerted to a potential scoring issue.

Conclusion: Expectation bias is ubiquitous. Utilizing video- and/or tele-conferencing to employ raters who are a) blinded to study visit number, b) different across study visits, appears to yield decreased placebo response and/or better signal detection. Likewise, error variance is ubiquitous with subjective outcome measures. Application of tablet-, smartphone- or laptop-based software to encourage use of SIGs, and reduce other interview and scoring errors in real time also shows promise.

Learning Objectives:

- The audience should understand expectation bias and error variance, their role in subjective endpoints, and factors that can increase/decrease them in the CNS clinical trial setting.
- The audience should learn about some new technologies that may reduce expectation bias and error variance in certain settings.

Literature References:

- Williams JBW, Kobak KA, Giller E, Reasner DS, Curry L, Detke MJ. Comparison of Site-Based Versus Central Ratings in a Study of Generalized Anxiety Disorder, *J Clin Psychopharm*, 2015, 35(6), 654-660.

- Shen JHQ, Zhao Y, Rosenzweig-Lipson S, Popp D, Williams JBW, Giller E, Detke MJ, Kane J. A 6-week Randomized, Double-blind, Placebo-controlled, Comparator Referenced Trial of Vabicaserin in Acute Schizophrenia, *J Psych Res*, 2014 Jun; 53, 14-22.

NEUROMODULATION WITH TRANSCRANIAL NEAR-INFRARED LIGHT: CONTROLLED EVIDENCE*

Paolo Cassano, Massachusetts General Hospital

Overall Abstract: Transcranial photobiomodulation (t-PBM) with near-infrared (NIR) light is a new treatment for psychiatric disorders. t-PBM penetrates deeply into the cerebral cortex, modulates cortical excitability and improves cerebral perfusion and oxygenation. t-PBM is mechanistically different from other modalities of neuromodulation, which typically employ electro-magnetic modulation of cortical neurons. Near-infrared light is absorbed by mitochondria; it boosts cerebral metabolism, promotes neuroplasticity and modulates endogenous opioids, while decreasing inflammation and oxidative stress. The safety of t-PBM has been demonstrated in a sample of acute 1,410 stroke patients. A procognitive effect was shown in healthy subjects and in patients with TBI and with dementia. An antidepressant and anti-anxiety effect have also been reported.

Specific Purpose: We address the question: is transcranial photobiomodulation with infrared light a new therapy for psychiatric disorders in need of further exploration?

Content: nearly all device-based therapies for psychiatric disorders are based on electromagnetic neuromodulation of the brain; we propose to discuss a completely novel approach to improve brain metabolism and therefore treat psychiatric disorders.

Methodology and Importance: lack of controlled-evidence has limited the reliability of the data presented on transcranial photobiomodulation; for the first time we propose a symposium primarily based on controlled data, both in humans and animal models.

Results: we have pooled several researcher groups who have worked on transcranial photobiomodulation in different subsets of subjects and we will present data on mood disorder and dementia patients.

Learning Objectives:

- Learn the mechanism of action of red and near-infrared light shed transcranially.
- Learn the potential clinical applications of transcranial photobiomodulation, based on controlled evidence.

TRANSCRANIAL PHOTOBIMODULATION FOR BRAIN DISORDERS*

Yingying Huang, Harvard Medical School/Massachusetts General Hospital

Individual Abstract: Transcranial photobiomodulation (tPBM) is a new approach to treat traumatic brain injury (TBI) and many other brain disorders in which NIR light is delivered to the head, and penetrates the scalp and skull to reach the brain. 810-nm laser was delivered by 1 or 3 daily applications to the heads of mice, with controlled cortical impact TBI.

Memory, learning, depression, anxiety were measured for 4 weeks. Mice were sacrificed and immunofluorescence studies carried out on their brains.

tPBM-treated mice had improved learning and memory, and less depression and anxiety up to 4 weeks. Treated mice had increased neuroprogenitor cells in the dentate gyrus of the hippocampus and subventricular zone at 7 days. Markers of neuron migration and neurotrophins (BDNF) were increased at 7 days, while synaptogenesis (formation of new connections between existing neurons) was increased in the cortex at 28 days.

We propose that tPBM can induce the brain to repair itself after injury. However its ability to induce neurogenesis and synaptogenesis suggests that PBM may have much wider applications to treat neurodegenerative and psychiatric disorders.

Learning Objectives:

- Understand the broad potential of tPBM at a molecular and cellular level in the brain.
- Realize that tPBM may be applied to traumatic brain disorders (stroke and TBI), neurodegenerative diseases (Alzheimer's and Parkinson's), and psychiatric disorders (depression and PTSD).

Literature References:

- Transcranial low-level laser therapy enhances learning, memory, and neuroprogenitor cells after traumatic brain injury in mice. Xuan W, Vatansever F, Huang L, Hamblin MR. *J Biomed Opt.* 2014;19(10):108003. doi: 10.1117/1.JBO.19.10.108003.
- Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. Xuan W, Agrawal T, Huang L, Gupta GK, Hamblin MR. *J Biophotonics.* 2015 Jun;8(6):502-11. doi: 10.1002/jbio.201400069.

COGNITIVE DEFICITS AND MITOCHONDRIAL DYSFUNCTION IN MOOD DISORDERS - THE RATIONALE FOR TRANSCRANIAL PHOTOBIMODULATION*

Dan Iosifescu, Nathan S Kline Institute/New York University School of Medicine

Individual Abstract: Background: Cognitive deficits are prevalent in mood disorders and have a major impact on subjects' ability to function. Specific studies have associated cognitive deficits with abnormal patterns of activation in specific brain areas (DLPFC, ACC). However, it is unclear how such deficits are related with biological changes in depression, such as mitochondrial dysfunction, nor what should be the optimal treatment.

Methods: We will present recent data from 50 unmedicated subjects with major depression (MDD; mean age: 43.4±13.6; 46% female) and 30 matched healthy volunteers (age 39.0±12.5; 36.6% female). All subjects received a phosphorus-31 magnetic resonance spectroscopy (31P MRS) scan with 84 voxels collected over the entire brain. We will also present data from several recent studies where transcranial photobiomodulation (t-PBM) with near-infrared (NIR) light, delivered over prefrontal area by a class IV laser in healthy volunteers and in MDD subjects, was used to test short-term effects on cognitive functions.

Results: Compared to healthy subjects, gray matter phosphocreatine (PCr) content was 5% higher in MDD subjects ($p < 0.04$), and white matter PCr was 4% reduced ($p = 0.03$). In independent studies, when compared to sham, single dose administrations of t-PBM in prefrontal areas in healthy and MDD subjects were associated with significant improvement in attention, working memory and executive function.

Conclusions: t-PBM with near-infrared light, which corrects mitochondrial dysfunction by up-regulating cytochrome-c-oxidase, may be associated with suggests transient improvement in

cognitive performance in healthy and depressed subjects. These data warrant rigorous testing t-PBM in repeated administration in mood disorders.

Learning Objectives:

- Discuss the prevalence of cognitive deficits of mitochondrial dysfunction in mood disorders.
- Learn the potential role of transcranial photobiomodulation as cognitive enhancer.

Literature References:

- Harper DG, Jensen JE, Ravichandran C, Perlis RH, Fava M, Renshaw PF, Iosifescu DV. Tissue Type-Specific Bioenergetic Abnormalities in Adults with Major Depression. *Neuropsychopharmacology*. 2017 Mar; 42(4): 876-885
- Cassano P, Petrie SR, Hamblin MR, Henderson TA, Iosifescu DV (2016): Review of transcranial photobiomodulation for major depressive disorder: targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. *NeuroPhotonics*. 3: 31404.

TRANSCRANIAL PHOTOBIMODULATION IN MAJOR DEPRESSIVE DISORDER*

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Individual Abstract: Background: Transcranial photobiomodulation (t-PBM) with red or near-infrared (NIR) light increases brain metabolism and neuroplasticity; it also modulates endogenous opioids, while decreasing inflammation and oxidative stress. Preliminary, uncontrolled studies suggested an antidepressant effect of t-PBM in subjects suffering from major depressive disorder (MDD).

Methods: We conducted a double-blind, sham-controlled study on the safety and efficacy of adjunct NIR t-PBM delivered to dlPFC twice a week in subjects with MDD. The treatment course was 8 weeks of t-PBM (Omnilux New U – LED, 830nm (NIR); 36.2mW/cm²; up to 65.2J/cm²; 3.7kJ per session or sham for a total of 16 sessions). The change in total score of the Hamilton depression rating scale (HAM-D17) from baseline to endpoint was the primary outcome measure (one-way unpaired t-test).

Results: Eighteen evaluable subjects out of 21 randomized were included in the analyses, having received at least 4 t-PBM (real or sham) sessions plus post-treatment assessments. There were no significant differences between groups at baseline. At endpoint, the mean change in HAM-D17 score in subjects receiving t-PBM NIR-mode was significantly greater than sham-mode, both in the overall sample (n=9 vs. 9 sham; Mean±SD = -11.7±7.47 vs. -5.3±7.03; LOCF, df=16, t=1.85, p=.04) and in completers (n=6 vs. 7 sham; Mean±SD = -15.7±4.41 vs. -6.1±7.86; df=11, t=2.62, p=.01). The effect size for the antidepressant effect of t-PBM was d=0.87. Further, t-PBM was well tolerated, with no serious adverse events reported.

Conclusions: t-PBM with near-infrared light could be a novel intervention for patients with MDD. Replication in larger samples is warranted.

Learning Objectives:

- Learn the potential use of transcranial near-infrared light as a novel treatment for mood disorders.
- Learn the side-effects profile and safety data on transcranial near-infrared light.

Literature References:

- Cassano P, Petrie SR, Hamblin MR, Henderson TA, Iosifescu DV (2016): Review of transcranial photobiomodulation for major depressive disorder: targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. *Neurophotonics*. 3: 31404.
- Cassano P, Cusin C, Mischoulon D, Hamblin MR, De Taboada L, Pisoni A, et al. (2015): Near-Infrared Transcranial Radiation for Major Depressive Disorder: Proof of Concept Study. *Psychiatry J*. 2015: 352979.

SIGNIFICANT IMPROVEMENT IN COGNITION IN MILD TO MODERATELY-SEVERE DEMENTIA CASES TREATED WITH TRANSCRANIAL PLUS INTRANASAL PHOTOBIMODULATION: CASE SERIES REPORT

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Individual Abstract: Objective: This case series investigated if patients with mild to moderately-severe dementia, mild cognitive impairment (MCI) or Alzheimer's Disease (AD) who had baseline Mini Mental State Exam (MMSE) scores of 10-24, would improve when treated with near-infrared (NIR) photobiomodulation (PBM) therapy. Background: Animal studies have suggested the potential of PBM to treat AD. Presumed mechanisms of action are increased adenosine-triphosphate and focal, vasodilation. Dysregulation of the brain's default mode network (DMN) has been associated with MCI and AD, suggesting that cortical nodes within the DMN are identifiable targets for PBM. Materials & Methods: This study used 810nm, 10Hz pulsed, light-emitting diode (LED) devices combining transcranial plus intranasal PBM to treat the cortical nodes of the DMN – e.g., mesial prefrontal, precuneus, angular gyri (transcranial PBM); and hippocampus (intranasal PBM). Five patients with mild to moderately-severe dementia, MCI or AD were entered into 12 weeks of active treatment followed by a 4-week, no treatment period. Patients were assessed with MMSE and Alzheimer's Disease Assessment Scale–cognitive (ADAS-cog) tests. The protocol involved weekly, in-clinic use of a transcranial plus intranasal PBM device; and daily at-home use of a separate, intranasal-only PBM device. Results: There was significant cognitive improvement after 12 weeks of PBM (MMSE, $p < 0.003$; ADAS-cog, $p < 0.023$). Fewer angry outbursts, better sleep, better daily functioning, less anxiety and wandering were reported. There were no negative side effects. Precipitous declines were observed during the 4-week, no treatment period, a possible problem for future studies. Here, following their completion of study participation each case was given his/her own PBM devices to keep. This case series is the first completed PBM case series to report significant, cognitive improvement in mild to moderately-severe dementia cases post-PBM. Conclusion: Results suggest that larger, controlled studies are warranted. PBM shows potential for home treatment of patients with dementia, MCI, AD.

Learning Objectives:

- To become aware of photobiomodulation for the treatment of dementia.
- To understand how photobiomodulation may enhance clinical outcomes for a variety of neurological and psychiatric conditions.

Literature References:

- Naeser MA, Saltmarche A, Krengel MH, Hamblin MR, Knight JA: Improved Cognitive Function After Transcranial, Light-Emitting Diode Treatments in Chronic, Traumatic Brain Injury: Two Case Reports. *Photomed and Laser Surgery* 2011; 29:5: 351–358

- Naeser MA, Zafonte R, Krengel MH, Martin PI, Frazier J, Hamblin MR, Knight JA, Meehan III WP, Baker EH: Significant Improvements in Cognitive Performance Post-Transcranial, Red/Near-Infrared Light-Emitting Diode Treatments in Chronic, Mild Traumatic Brain Injury: Open-Protocol Study. J Neurotrauma 2014; 31:1008–1017