ABSTRACT BOOK

Loews Miami Beach Hotel
May 29–June 1, 2018

ASCP 2018 ANNUAL MEETING:
Treatment of Psychiatric Illness Across the Lifespan

ASCP
American Society of Clinical Psychopharmacology

www.ASCPMeeting.org

Tuesday, May 29, 2018

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

ACTIVE UPDATE: REDUCTION IN WORLD HEALTH ORGANIZATION (WHO) DRINKING RISKS LEVEL AS A PRIMARY ENDPOINT FOR ALCOHOL TREATMENT TRIALS

Stephanie O'Malley, Yale University School of Medicine

Overall Abstract: Alcohol use disorder (AUD) is a devastating disorder, responsible for a myriad of medical, psychological, social, economic, and personal problems. Currently, three medications (disulfiram, naltrexone, and acamprosate) have been approved by the Food and Drug Administration (FDA) to treat AUD. However, because of the heterogeneity of AUD, these medications do not work for everyone. Therefore, efforts continue to discover and develop new, more effective medications. As part of the drug development process, FDA approval is necessary for a medication to become widely accessible. The FDA has identified two primary dichotomous endpoints for defining successful clinical trial outcomes in pivotal phase 3 trials: total abstinence and the percent of subjects with no heavy drinking days. Although these two measures are excellent at capturing incidents of abstinence and low risk-drinking, they do not enable one to accurately assess reductions in drinking. Moreover, recent research suggests that a drinking reduction goal is the vastly endorsed by clinical trial participants and patients in clinical programs, thereby broadening treatment acceptance and opportunities for the public at large. A new endpoint, that reflects a reduction in drinking, has been identified –¬ a reduction in the World Health Organization's (WHO) risk drinking levels. These drinking categories include very high risk, high risk, moderate risk, and low risk levels. In this panel session, several presentations will demonstrate that reduction in the WHO risk drinking levels results in clear improvements in how individuals with AUD feel and function – endpoint criterion endorsed by the FDA. The presentations will provide detailed analyses of epidemiological and multisite alcohol clinical trial studies, showing the validity and practicability of this endpoint.

Learning Objectives:

1. To understand the process of validating a new alcohol treatment endpoint.
2. To determine the practicality of the reduction in WHO risk drinking level endpoint across several alcohol clinical trials.

CHANGE IN WHO RISK DRINKING LEVELS AND CLINICAL OUTCOMES: FINDINGS FROM THE U.S. GENERAL POPULATION

Deborah Hasin, Columbia University

Individual Abstract: WHO risk drinking levels may be informative endpoints for alcohol clinical trials, but reduction in very high or high levels should result in individuals feeling and functioning better. Little is known about the relationship of change in WHO risk drinking levels to prospectively measured change in risk for alcohol and drug disorders, psychiatric disorders, functioning, liver disease and AUDIT-C screening scores. Data were analyzed from current drinkers in the NESARC who were followed up and re-evaluated 3 years later (N=22,005). Reduction from very high WHO risk levels to high, moderate or low levels was accompanied by significantly reduced risk for alcohol, drug and psychiatric disorders, functioning, liver

disease and AUDIT-C scores. Reductions in WHO risk from high levels was accompanied by reduction in risk for some but not all of these outcomes. The findings support the use of the WHO risk drinking levels as informative endpoints for clinical trials of treatments for alcohol use disorders, especially in particularly heavy drinkers.

Learning Objectives

1. To identify the relationship of WHO risk drinking levels to substance use and psychiatric disorders in a national sample.
2. To identify the relationship of WHO risk drinking levels to functioning, liver disease and AUDIT-C scores.

Literature References

1. Hasin DS, Wall M, Witkiewitz K, Kranzler HR, Falk D, Litten RZ, Mann K, O'Malley SS, Scodes J, Robinson RL, Anton RF. Change in Non-Abstinent World Health Organization Risk Drinking Levels and Alcohol Dependence: A 3-Year Follow-Up Study in the United States General Population. Lancet Psychiatry. 2017 Jun; 4(6):469-476. PubMed PMID: 28456501.
2. Witkiewitz K, Hallgren KA, Kranzler HR, Mann KR, Hasin DS, Falk DE, Litten RZ, O'Malley SS, & Anton RF. Clinical Validation of Reduced Alcohol Consumption after Treatment for Alcohol Dependence using the World Health Organization Risk Drinking Levels. Alcoholism: Clinical and Experimental Research. 2017 Jan;41(1):179-186. PubMed PMID: 28019652; PubMed Central PMCID: PMC5205540.

THE RELATIONSHIP OF WORLD HEALTH ORGANIZATION DRINKING RISK LEVELS TO HOW PATIENTS "FEEL AND FUNCTION" IN AN ALCOHOL CLINICAL TRIAL

Katie Witkiewitz, University of New Mexico

Individual Abstract: The goal of the current study was to examine the correspondence between levels of alcohol consumption and experiences of drinking-related consequences, mental health, blood pressure, and liver function tests during treatment among individuals receiving treatment for alcohol dependence in the COMBINE study (n=1383). After controlling for numerous demographic variables and clinical characteristics assessed at baseline, results indicated reductions in WHO risk levels were associated with significantly fewer alcohol related consequences, greater mental health, and improvements in physical health functioning, including reduced blood pressure and better liver function. Importantly, even a one level decrease in WHO risk drinking levels predicted statistically and clinically significant decreases in the risk of experiencing a variety of alcohol related consequences, improvements in mental health, and improvements in blood pressure and liver function. The reduction in risk of experiencing alcohol related consequences and improvements in mental and physical health were greater for each additional decrease in WHO risk drinking level. The results from the current study provide evidence of reductions in WHO risk levels as a viable alternative to abstinence as an endpoint for alcohol clinical trials. The paper will also discuss the application of WHO risk levels in clinical practice and provide clear guidance for clinicians on the targets for alcohol risk reduction that are most likely to be associated with meaningful reductions in alcohol related consequences and improvements in mental and physical health.

Learning Objectives

1. Compare various drinking consequences with respect to levels of drinking at varying risk levels of drinking in clinical trial data.

2. Describe the correspondence between World Health Organization drinking risk level reduction and mental and physical health functioning.

Literature References

1. Witkiewitz K, Hallgren KA, Kranzler HR, Mann KF, Hasin DS, Falk DE, Litten RZ, O'Malley SS, Anton RF: Clinical validation of reduced alcohol consumption after treatment for alcohol dependence using the World Health Organization risk drinking levels. Alcohol. Clin. Exp. Res. 2017; 41(1):179-186.
2. Hasin DS, Wall M, Witkiewitz K, Kranzler HR, Falk D, Litten R, Mann K, O'Malley SS, Scodes J, Robinson RL, Anton R: Change in non-abstinent WHO drinking risk levels and alcohol dependence: A 3 year follow-up study in the US general population. The Lancet Psychiatry 2017; 4(6):469-476.

MEASURING RESPONSE TO ALCOHOL PHARMACOTHERAPY: EFFICACY ENDPOINTS BASED ON REDUCTIONS IN THE WORLD HEALTH ORGANIZATION (WHO) RISK LEVELS OF ALCOHOL CONSUMPTION

Daniel Falk, NIAAA/NIH

Individual Abstract: Objective: Alcohol consumption endpoints are the primary measure of efficacy in pharmacotherapy trials for the treatment of alcohol use disorder (AUD). The US Food and Drug Administration (FDA) recognizes two endpoints for pivotal trials: total abstinence and no heavy drinking (FDA, 2015) as surrogates of how the patient feels and functions. However, additional harm reduction-based endpoints would benefit the field if shown to be sensitive to the effects of treatment while still being clinically meaningful. The current study evaluated the sensitivity of two endpoints based on the World Health Organization (WHO) risk levels of alcohol consumption (EMA, 2010): the percentage of participants who reduce their risk by at least two or one levels (WHO 2- or 1-level shift endpoints)

Methods: Data were obtained from 3 multisite randomized, placebo controlled trials of 3 different medications: naltrexone (Anton et al., 2006), varenicline (Litten et al., 2013), and topiramate (Johnson et al., 2007). Effect sizes comparing placebo to active medication within each study were calculated with Cohen's h for the WHO shift endpoints and compared to effect sizes obtained using abstinence and no heavy drinking as endpoints. Treatment effects for the WHO shift endpoints summarized across different periods of observation were also evaluated.

Results: Across studies, the percentage of participants classified as a responder was lowest for abstinence followed by no heavy drinking, WHO 2-level shift, and WHO 1-level endpoints. The magnitude of the treatment effects observed for the WHO 2- and 1-level shift endpoints were comparable to those obtained using traditional responder definitions. Across studies, effects sizes obtained for WHO shift endpoints were larger with the inclusion of a grace period.

Conclusion: These findings suggest that the WHO 2- and 1- shift endpoints may be worthy of further development as measures in alcohol pharmacotherapy trials. In addition, the finding that the WHO shift response measures capture improvements experienced by more patients than abstinence and no heavy drinking may be attractive to patients and providers.

Learning Objectives

1. To gain familiarity of the various endpoints used to assess the efficacy of medications in alcohol pharmacotherapy trials.

2. To gain an understanding of sensitivity of the new WHO endpoints to detect treatment effects in two alcohol pharmacotherapy trials.

Literature References

1. European Medications Agency (EMA). 2010. Guideline on the development of medicinal products for the treatment of alcohol dependence. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf (accessed November 13, 2017).
2. Food and Drug Administration (FDA). 2015. Alcoholism: developing drugs for treatment. Guidance for industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM433618.pdf (accessed November 13, 2017).

HERBAL AND NUTRACEUTICAL AGENTS FOR SCHIZOPHRENIA: RECENT CLINICAL TRIALS*

Stephen Marder, Semel Institute at UCLA

Overall Abstract: Herbal and nutraceutical agents exhibit anti-inflammatory, immunomodulatory, anti-apoptotic, anti-oxidant, and NMDA-receptor potentiation among other properties that are potentially useful in the treatment of schizophrenia. Moreover, the above-mentioned mechanisms are not addressed by dopamine-receptor antagonists, which are the mainstay of treatment. Furthermore, these agents are relatively inexpensive. Finally, the side-effect profile is relatively benign for many of these agents. This session will review randomized control trials (RCTs) from three sites that evaluated the effectiveness of herbal or nutraceutical agents added to antipsychotic medications in individuals with schizophrenia. In each case, the speaker will present data indicating how these compounds might affect targets in brain and the clinical outcomes obtained in the RCTs. Jonathan Wynn from University of California Los Angeles will present a study that added curcumin to antipsychotics. Although effects on clinical outcomes were not significant, subjects treated with curcumin demonstrated increased levels of brain-derived neurotrophic growth factor (BDNF) suggesting that curcumin may enhance neuroplasticity. Dr. Jessica Gannon from the Western Psychiatric Institute and Clinic at the University of Pittsburgh will present the results of a randomized, placebo-controlled clinical trial, in which a standardized extract of Withania somnifera (WSE), also known as Ashwagandha, was added to the medication regimens of outpatients with schizophrenia who were experiencing symptom exacerbations. Treatment with WSE resulted in significantly greater reductions in negative, general and total symptoms, but not positive symptoms, when compared to placebo. Scores on the perceived stress scale were also improved with WSE. Dr. Dean Salisbury from the Western Psychiatric Institute and Clinic at the University of Pittsburgh will present preliminary data suggesting that adjunctive treatment with the same extract of Withania somnifera appears to improve brain function as reflected in the auditory mismatch negativity neurophysiological response, a brainwave that is greatly impaired in schizophrenia. Dr. Alan Breier from the Indiana University School of Medicine will present the results of a 12-month, double-blind, placebo-controlled trial of N–Acetyl Cysteine (NAC) in subjects with early stage psychosis. NAC demonstrated significant improvement in PANSS total, Cognitive/Disorganized factor and Negative Symptom factor scores, but failed to improve PANSS positive symptoms and cognition as assessed by the BACS. Baseline cortical thickness was associated with NAC-related improvement in total

symptoms, but NAC did not prevent progressive brain mass loss over the 12-month study period.

Learning Objectives

1. To inform the viewers about the clinical effects of selected herbals and nutraceuticals.
2. To inform the viewers about the effects of selected herbals and nutraceuticals on the brain.

A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF CURCUMIN NANOPARTICLES ON COGNITION AND BRAIN DERIVED NEUROTROPHIC FACTOR IN SCHIZOPHRENIA

Jonathan Wynn, VA Greater Los Angeles Healthcare System/UCLA

Individual Abstract: Curcumin is a polyphenolic compound derived from the spice turmeric (Curcuma longa) with potential as a complementary treatment for people with schizophrenia. Curcumin has been reported to have anti-oxidant, anti-inflammatory, neuroprotective, and pro-cognitive properties, as well as be able to increase levels of brain-derived neurotrophic factor (BDNF). Abnormalities in neurotrophic factors have been hypothesized to contribute to many clinical features of schizophrenia (1). BDNF has been a focus of investigation due to its role in neurogenesis, neuroplasticity, and learning and memory. BDNF levels are consistently lower in schizophrenia. Serum levels of BDNF have shown positive associations with cognitive functioning in patients with schizophrenia. Thus, BDNF might be a mediator for beneficial effects on cognition in schizophrenia. In the current study, we hypothesized that curcumin would increase BDNF levels and improve cognitive performance in patients with schizophrenia.

We examined the effects of curcumin in patients with a DSM-5 diagnosis of schizophrenia in an 8-week randomized, double-blind, placebo-controlled study, assessing BDNF levels, clinical symptoms, and measures of social and non-social cognition. Seventeen patients received curcumin (360 mg/day) and 19 patients received matched placebo. All patients were on a stabilized dose of antipsychotic medication. Participants received clinical, cognitive (social and non-social), and blood draws at baseline (prior to study treatment), and at 4- and 8-weeks post baseline. The Brief Psychiatric Rating Scale and the Clinical Assessment Interview for Negative Symptoms were used for symptom ratings. We assessed non-social cognition with the MATRICS Consensus Cognitive Battery (MCCB), and social cognition with an empathic accuracy task. For analyses of treatment effects, the primary effect of interest was the treatment-by-time interaction.

There were no significant differences between groups on age, personal education, parental education, body mass index, or smoking status. For BDNF serum levels, there were no significant main effects of treatment or time. However, the treatment X time interaction was significant, $F(1,69) = 4.23$, $p = 0.043$. Patients on curcumin showed increased levels of BDNF relative to baseline, whereas patients on placebo showed declines relative to baseline. For the MCCB overall composite score, empathic accuracy task performance, and clinical symptom ratings, the treatment X time interaction was not significant.

This is the first randomized, double-blind, placebo-controlled study evaluating the effects of curcumin on BDNF, clinical, and cognitive measures in patients with schizophrenia. In this study curcumin increased BDNF levels over the 8-week treatment period as compared to placebo. These results demonstrate that curcumin may have a reliable biomarker in its effects on BDNF, but did not show more distal effects on cognition or clinical symptoms for patients

with schizophrenia. These results are promising regarding a proximal biomarker, BDNF, and may have long-term benefits for cognition and symptoms that would not be observable in an 8-week trial. Because the development of schizophrenia has been linked to increased inflammatory response, oxidative stress, and abnormal neural pruning (2), a therapeutic agent that alleviates one or more of these by increasing BDNF could protect processes (e.g., poor learning, memory, neuroplasticity) impacted by the disease.

Learning Objectives

1. Attendees at this session will understand the rationale for studying the effects of curcumin in schizophrenia.
2. Attendees will understand the effects of curcumin on BDNF.

Literature References

1. Buckley PF, Mahadik S, Pillai A, Terry A, Jr. Neurotrophins and schizophrenia. Schizophr Res. 2007;94:1-11.
2. Barron H, Hafizi S, Andreazza AC, Mizrahi R. Neuroinflammation and Oxidative Stress in Psychosis and Psychosis Risk. Int J Mol Sci. 2017;18.

EFFECTS OF 12-MONTH, DOUBLE-BLIND N-ACETYL CYSTEINE ON SYMPTOMS, COGNITION AND BRAIN MORPHOLOGY IN EARLY PHASE SCHIZOPHRENIA

Alan Breier, Indiana University School of Medicine

Individual Abstract: Currently approved medications for schizophrenia are relatively ineffective for negative symptoms and cognitive impairment. N-Acetyl Cysteine (NAC) is a neuroprotective agent that has been shown to improved general symptom scores, negative symptoms and cognitive impairment, but failed to improve positive symptoms in patients with schizophrenia. In this study, we assessed the effects NAC (3600 mg/day) in a 52-week, double-blind, placebo controlled trial on symptoms and cognition in early phase schizophrenia (N=60). In addition, NAC has properties, including effects on oxidative stress, inflammation and glutamatergic modulation, that have all been hypothesized to contribute to progressive brain mass loss (PBML) which has been consistently observed in schizophrenia with particularly pronounced effects in early phase psychosis. In the context of the clinical trial, we explored the effects of NAC on brain morphology. NAC significantly improved (time x group) PANSS total ($F=14.7$, $p<0.001$), negative ($F=5.1$, $p=0.024$) and disorganized thought ($F=13.7$, $p<0.001$) symptom scores. NAC failed to improve PANSS positive symptoms and BACS cognitive scores. In preliminary analyses, baseline right ($r= -0.48$, $p=0.041$) and left ($r= -0.45$, $p=0.018$) total cortical thickness, and thickness in other cortical regions, were associated with NAC related improvement in PANSS total scores, but NAC, as compared to placebo, did not significantly impact brain morphology over the study treatment period. These results support previous findings of NAC efficacy for total and negative symptoms, and failure to improve positive symptoms. Preliminary results suggest that NAC's symptom effects may be related to structural integrity. Future studies are needed to confirm these findings.

Learning Objectives

1. Achieve an understanding of the scientific rationale for the use of neuroprotective agents in the treatment of schizophrenia.
2. Achieve an understanding of the clinical trial findings of N-Acetyl Cysteine (NAC) in schizophrenia.

Literature References

1. Berk, M., Copolov, D., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., Anderson-Hunt, M., Judd, F., Katz, F., Katz, P., Ording-Jespersen, S., Little, J., Conus, P., Cuenod, M., Do, K. Q., & Bush, A. I. (2008). N-acetyl cysteine as a glutathione precursor for schizophrenia--a double-blind, randomized, placebo-controlled trial. Biol Psychiatry, 64, 361-8.
2. Farokhnia, M., Sabzabadi, M., Pourmahmoud, H., Khodaie-Ardakani, M. R., Hosseini, S. M., Yekehtaz, H., Tabrizi, M., Rezaei, F., Salehi, B., & Akhondzadeh, S. (2014). A double-blind, placebo controlled, randomized trial of riluzole as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia. Psychopharmacology (Berl), 231, 533-42.

WITHANIA SOMNIFERA AS AN ADJUVANT TREATMENT OF EXACERBATED SCHIZOPHRENIA: A NOVEL APPROACH TO NEGATIVE SYMPTOMS?

Jessica Gannon, University of Pittsburgh School of Medicine

Individual Abstract: There is a growing body of evidence supporting broad use of Withania somnifera (WSE), also known as Ashwaghanda, in mental illness, but little is known about WSE's potential efficacy in schizophrenia. WSE is an adaptogen widely used in Ayurvedic medicine in India for well over a thousand years. Common use targets normalization of bodily processes and increasing patients' resistance to stress and disease. Clinical trials and rodent models have suggested promise in the treatment of many neuropsychiatric conditions, including Generalized Anxiety Disorder, Alzheimer's Dementia, Obsessive Compulsive Syndrome, as well as for mitigation of chronic stress. WSE has further been studied as an adjuvant, pro-cognitive agent in Bipolar Disorder. Animal studies have demonstrated WSE's immunomodulating and anti-inflammatory properties, enhancing type-1 immune response and cytokine production, modulating production of acute phase reactants, and inhibiting the COX-2 enzyme as well as NF-kB inflammatory signaling pathways. These properties suggest potential clinical utility in at least subgroups of patients with schizophrenia, where immune-inflammatory dysregulation leads to imbalances of type-1 and type-2 immunity, elevated levels of inflammatory proteins, and downstream effects on neurotransmission (linked more directly to clinical symptomatology). As such, we enrolled exacerbated patients with schizophrenia spectrum disorders in a 12-week randomized, placebo-controlled, double-blind study to determine if adjunctive treatment with a 1000mg of standardized extract of WSE would improve measures of psychopathology and stress. Efficacy data was obtained on sixty-six patients. Primary outcomes were change from baseline to end of treatment in the Positive and Negative Syndrome Scale (PANSS total, positive, negative, and general symptoms). Secondary outcomes evaluated stress, using the Perceived Stress Scale (PSS) as well as the inflammatory indices S100B and C - reactive protein (CRP). Beginning at 4 weeks, and continuing to the end of treatment, WSE produced significantly greater reductions in PANSS negative, general and total symptoms (Cohen's d: 0.83, 0.76, 0.83), but not positive symptoms, when compared to placebo. PSS scores improved significantly with WSE treatment compared to placebo (Cohen's d: 0.58). CRP and S100B declined more in the WSE group but were not significantly different from placebo. Adverse events were mild to moderate and transient; somnolence, epigastric discomfort, and loose stools were more common with WSE. Taken together, while the mechanism of its clinical efficacy requires more exploration, these findings suggest that WSE may have promise in exacerbated schizophrenia, particularly in the treatment of negative and general symptoms and associated stress.

Learning Objectives

1. Recall some of the suggested mechanisms of clinical efficacy of Withania somnifera in the treatment of neuropsychiatric disorders.
2. Evaluate the evidence for Withania somnifera as a potential adjuvant treatment of schizophrenia.

Literature References

1. Steullet P, Cabungcal JH, Monin A, et al: Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A 'central hub' in schizophrenia pathophysiology? Schizophr Res 2016; 176: 41–51.
2. Chengappa KNR, Bowie CR, Schlicht P, et al: Randomized Placebo-Controlled Adjunctive Study of an Extract of Withania Somnifera for Cognitive Dysfunction in Bipolar Disorder. J Clin Psychiatry 2013; 74(11): 1076-1083.

ASHWAGANDA MAY RECOVER BRAIN FUNCTION IN LONG-TERM SCHIZOPHRENIA

Dean Salisbury, University of Pittsburgh School of Medicine

Individual Abstract: Schizophrenia is associated with profound auditory abnormalities, from complex verbal hallucinations to more basic sensory processing deficits. One neurophysiological sign of automatic auditory change detection, a key process in altering and orienting to potential environmental threat, the mismatch negativity brainwave, is robustly impaired, and is one of the largest deficits observed in the disorder. Here we examined whether the antioxidant and anti-inflammatory adjunctive medication Ashwaganda improved mismatch negativity in long-term schizophrenia.

Eleven participants from a larger double-blind study of Ashwaganda were tested for mismatch negativity. Rare pitch-deviant (10%, 1.2 kHz, 50 msec duration) and duration -deviant (10%, 1 kHz, 100 msec duration) tone pips were presented among standard tones (80%, 1 kHz, 50 msec duration) passively as participants watched a silent video. EEG was recorded and processed offline to extract the event-related potentials to each tone. The difference between the standard and deviant tones was calculated by subtraction of the averaged event-related potentials to the standard tones from those to the respective deviant tones. This preliminary analysis focused on duration deviant mismatch negativity (dMMN), as that response has shown the largest deficit in schizophrenia, and is thought to be associated with trait liability to the disorder.

While the 6 participants on placebo showed no change in mismatch negativity amplitude, the individuals receiving Ashwaganda showed a larger mismatch response after treatment. This was reflected in a trend level interaction between treatment (Ashwaganda, placebo) and time of testing (protocol entrance, end of treatment).

Although very preliminary, these data suggest that adjunctive treatment with Ashwaganda may recover some of the neurophysiological auditory processing deficits observed in schizophrenia. We hypothesize this action is due to recovery of parvalbumin interneurons silenced by neuro-inflammatory processes induced by oxidative stress, in turn caused by chronic antagonism at the glutamate NMDA-receptor. If this is replicated in a larger sample, it would provide new pharmacologic treatment option that may treat deficits in the disorder not currently ameliorated by dopamine-antagonist medication that are successful in treating positive symptoms but not negative or cognitive symptoms.

Learning Objectives

1. Understand the processes reflected in the mismatch negativity brainwave.
2. Understand the circuit abnormality potentially targeted by Ashwaganda as it impacts mismatch negativity.

Literature References

1. Salisbury, D. F., Kuroki, N., Kasai, K., Shenton, M. E., & McCarley, R. W. (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. Archives of general psychiatry, 64(5), 521-529.
2. Behrens, M. M., & Sejnowski, T. J. (2009). Does schizophrenia arise from oxidative dysregulation of parvalbumin-interneurons in the developing cortex? Neuropharmacology, 57(3), 193-200. Chicago.

IDENTIFYING MODERATORS OF ANTIDEPRESSANT TREATMENT AND STRATEGIES TO REDUCE PLACEBO RESPONSE: FINDINGS FROM THE EMBARC STUDY*

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: Treatment decisions for patients with major depressive disorder (MDD) continue to be based on clinical factors. This results in multiple treatment trials to attain adequate symptomatic control for a majority of patients with MDD. Unsurprisingly, most patients stay on ineffective medications for too long, switch treatments too early, or simply drop out of care. There is an urgent need to personalize antidepressant treatments by maximizing the likelihood of improvement and minimizing the risk of adverse events. Additionally, novel treatments are needed as over a third of patients with MDD fail to respond to currently available antidepressant treatments. The increasing placebo response rates in clinical trials over the last few decades have significantly limited the development of novel antidepressant medications. This symposium will present findings from the recently completed Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study which included comprehensive behavioral, neuroimaging, electrophysiologic, and clinical assessments to identify differential predicts of response to sertraline versus placebo.

The first presentation will focus on behavioral measures of hedonic capacity and personality traits to compute a personalized advantage index which predicts differential improvement with sertraline, as compared to placebo, in patients with MDD. The second presentation will elucidate the neural pathways underlying anhedonia in MDD patients and their association with differential antidepressant treatment outcome. The third presentation will systematically explore 291 clinical, behavioral, cognitive, electrophysiologic and neuroimaging markers using advanced variable selection methods to develop a clinical calculator to identify placebo responders with high sensitivity and specificity. The fourth presentation will focus on arterial spin labeling (ASL) and resting state functional magnetic resonance imaging (rsfMRI) moderators of differential outcomes to sertraline versus placebo.

Learning Objectives

1. Identify brain regions which are involved in pathophysiology of depression and in mediating response to antidepressant medications.

2. Implement clinical, behavioral and neuroimaging tools to reduce placebo response rate in clinical trials.

SYSTEMATIC EXPLORATION OF CLINICAL, SOCIODEMOGRAPHIC, ELECTROPHYSIOLOGIC AND NEUROIMAGING MARKERS TO PREDICT PLACEBO RESPONSE: FINDINGS FROM EMBARC STUDY

Manish Jha, UT Southwestern

Individual Abstract: Background: One in three patients with major depressive disorder (MDD) report symptomatic improvement with placebo in clinical trials. Rising placebo response rate over the last few decades has contributed to failure of novel antidepressant medications in Phase 2 and 3 clinical trials. Strategies to mitigate the effect of rising placebo response rates have focused on increasing sample sizes and modifying study design, with limited success. Clinical trial efficiency can be improved by identifying and excluding or controlling for individuals with high likelihood of responding to placebo.

Methods: Data for this report is based on participants of Establishing Moderators and Biosignatures for Antidepressant Response in Clinical Care (EMBARC) study who were randomized to placebo arm (n=141). Elastic net was used to evaluate a total of 291 baseline variables that span clinical, behavioral, electrophysiological, brain structure, brain connectivity, and brain regional activity features in order to identify a parsimonious set of variables that predicted the depression severity at week 8. To account for missing values, 100 imputed datasets were created, and elastic net was repeated in each of these datasets. Variables that were retained by elastic net in at least 50% of the imputed datasets were then used in Bayesian multiple linear regression analysis to simultaneously predict depression level at exit, the probability of response, and the probability of remission.

Results: Lower baseline depression severity, younger age, less anxious arousal and neuroticism, and higher average theta current density in the rostral anterior cingulate predicted higher likelihood of improvement with placebo. No neuroimaging variable was retained by the elastic net models across the 100 imputed datasets. A Bayesian calculator incorporating variables predictive of placebo response was able to predict remission (AUC=0.76) and response (AUC=0.75) with high degree of accuracy.

Conclusion: Easy to measure clinical, behavioral and electrophysiologic assessments can be used to identify responders to placebo with high degree of accuracy. Implementation of a calculator based on these findings can be incorporated in screening process to reduce placebo response rates.

Learning Objectives

1. Recognize the impact of rising placebo response rate in clinical trials of antidepressant medications.
2. Identify pre-treatment markers that predict placebo response with a high rate of accuracy.

Literature References

1. Trivedi MH, McGrath PJ, Fava M, Parsey RV, Kurian BT, Phillips ML, Oquendo MA, Bruder G, Pizzagalli D, Toups M, Cooper C, Adams P, Weyandt S, Morris DW, Grannemann BD, Ogden RT, Buckner R, McInnis M, Kraemer HC, Petkova E, Carmody TJ, Weissman MM. Establishing moderators and biosignatures of

antidepressant response in clinical care (EMBARC): Rationale and design. Journal of psychiatric research. 2016;78:11-23.
2. Papakostas GI, Østergaard SD, Iovieno N. The nature of placebo response in clinical studies of major depressive disorder. The Journal of clinical psychiatry. 2015;76:456-466.

PERSONALIZED PREDICTION OF ANTIDEPRESSANT VERSUS PLACEBO RESPONSE: EVIDENCE FROM THE EMBARC STUDY

Christian Webb, Harvard Medical School McLean Hospital

Individual Abstract: Importance: Meta-analyses reveal that overall differences in depressive symptom improvement between antidepressants and placebo are often small. Major Depressive Disorder (MDD) is a highly heterogeneous condition in terms of symptom presentation and, likely, underlying pathophysiology. Accordingly, it may be that only certain subsets of those with MDD are well-suited to antidepressants. A potentially fruitful approach to parsing this heterogeneity is to focus on promising endophenotypes of depression, such as neuroticism, anhedonia and cognitive control deficits.
Objective: To examine whether the combination of machine learning with the recently published Personalized Advantage Index (PAI) approach can generate individualized treatment recommendations on the basis of endophenotype profiles coupled with clinical and demographic characteristics previously linked with antidepressant response.
Design: Randomized clinical trial (RCT) enrolling MDD outpatients.
Setting: Multi-center study at four university hospitals.
Participants: Non-psychotic outpatients with chronic or recurrent MDD (18-65 years). Six hundred and twenty patients were screened, 299 were randomized, and 216 had usable data for analyses.
Intervention: Eight-week RCT of sertraline versus placebo.
Main Outcome(s): Week eight 17-item Hamilton Rating Scale for Depression (HRSD-17) score.
Results: Five pre-treatment variables moderated treatment response (neuroticism, cognitive control [Flanker accuracy interference effect], depressive symptom severity, age, and employment status). Across 1000 iterations of a 10-fold cross-validation, the PAI model predicted that 31% of the sample would exhibit a clinically meaningful advantage (post-treatment HRSD difference ≥ 3) with sertraline relative to placebo. Critically, although there were no overall outcome differences between treatment groups (d= .15), those identified as optimally suited to sertraline at pre-treatment had better week 8 HRSD scores if they were randomized to SSRI (10.7) than placebo (14.6)(d= .56). Conversely, those predicted by the PAI to be optimally suited to placebo (18%) had better outcomes with placebo (7.8) than sertraline (13.0)(d= .94).
Conclusions and Relevance: A subset of MDD patients optimally suited to sertraline can be identified on the basis of endophenotypes, combined with clinical and demographic characteristics. This model needs to be tested prospectively before it can be used to inform treatment selection. However, these findings demonstrate the potential for precision medicine to improve individual outcomes through algorithm-guided treatment recommendations.

Learning Objectives

1. Be able to define a prognostic (i.e., treatment non-specific) vs. a prescriptive (i.e., moderator) predictor of symptom improvement.
2. Be able to identify pre-treatment patient characteristics that predict greater depressive symptom improvement to SSRIs relative to placebo.

Literature References

1. DeRubeis RJ, Cohen ZD, Forand NR, et al. The Personalized Advantage Index: Translating Research on Prediction into Individualized Treatment Recommendations. A Demonstration. PLOS ONE. 2014;9(1):e83875. doi:10.1371/journal.pone.0083875.
2. Webb CA, Dillon DG, Pechtel P, et al. Neural Correlates of Three Promising Endophenotypes of Depression: Evidence from the EMBARC Study. Neuropsychopharmacology. 2016;41(2):454-463. doi:10.1038/npp.2015.165.

EXAMINATION OF REWARD-RELATED VENTRAL STRIATAL ACTIVITY IN RELATION TO TREATMENT RESPONSE IN MAJOR DEPRESSIVE DISORDER

Tsafrir Greenberg, University of Pittsburgh School of Medicine

Individual Abstract: Abnormalities in reward neural circuitry centered on the ventral striatum (VS) and medial prefrontal cortex have been reported in major depressive disorder (MDD). However, few studies have examined the extent to which reward-related neuroimaging measures predict antidepressant treatment response. We examined the relationship between reward expectancy (RE) and prediction error (PE) related right VS activity and treatment response in individuals with MDD recruited for the EMBARC study, a large multi-site placebo-controlled clinical trial of sertraline (SERT).

Participants were 134 unmedicated individuals with MDD who completed two functional magnetic resonance imaging (fMRI) sessions, at baseline and one week after treatment onset, while performing a reward task. We examined reward expectancy (RE) and prediction error (PE) related right ventral striatal (VS) activity in relation to treatment response (at week 8) to sertraline and placebo. Treatment response at week 8 was assessed with the Clinical Global Improvement scale and symptom reduction was measured weekly using the Hamilton Rating Scale for Depression (HRSD).

A 2 (condition: RE, PE) × 2 (session: 1, 2) × 4 (group: SERT responders, SERT non-responders, placebo responders, placebo non-responders) ANOVA showed a significant session by group interaction, ($F= 2.751$, $p= .045$) and a trend for a condition × session by group interaction ($F= 2.324$, $p= .078$). SERT responders and placebo non-responders showed the normal pattern of VS activity reduction across scanning sessions that we previously reported. By contrast, SERT non-responders and placebo responders, showed an increase in VS activity from session 1 to session 2. These differential VS response patterns in SERT responders and SERT non-responders were also observed when controlling for age, sex, education, anxiety symptoms, and depression severity. Additional mixed model analyses examining the relationship between reward measures and weekly HRSD scores support differences in rate of symptom reduction between the two treatment groups.

These findings suggest that abnormal functioning of dopaminergically-modulated reward circuitry may characterize sertraline non-responders but not sertraline responders.

Learning Objectives

1. Provide background regarding the importance of reward learning to MDD.
2. Discussion of specific reward-related neural measures in relation to treatment response.

Literature References

1. Chase HW, Fournier JC, Greenberg T, Almeida JR, Stiffler R, Zevallos CR, Aslam H, Cooper C, Deckersbach T, Weyandt S, Adams P, Toups M, Carmody T, Oquendo MA, Peltier S, Fava M, McGrath PJ, Weissman M, Parsey R, McInnis MG, Kurian B, Trivedi MH, Phillips ML. Accounting for Dynamic Fluctuations across Time when Examining fMRI Test-Retest Reliability: Analysis of a Reward Paradigm in the EMBARC Study. PLoS One. 2015;10(5):e0126326.
2. Greenberg T, Chase HW, Almeida JR, Stiffler R, Zevallos CR, Aslam HA, Deckersbach T, Weyandt S, Cooper C, Toups M, Carmody T, Kurian B, Peltier S, Adams P, McInnis MG, Oquendo MA, McGrath PJ, Fava M, Weissman M, Parsey R, Trivedi MH, Phillips ML. Moderation of the Relationship Between Reward Expectancy and Prediction Error-Related Ventral Striatal Reactivity by Anhedonia in Unmedicated Major Depressive Disorder: Findings From the EMBARC Study. Am J Psychiatry. 2015;172(9):881-91.

IDENTIFYING PREDICTORS OF ANTIDEPRESSANT TREATMENT RESPONSE IN MAJOR DEPRESSIVE DISORDER USING RESTING-STATE BRAIN IMAGING

Crystal Cooper, The University of Texas Southwestern Medical Center

Individual Abstract: Background: Major depressive disorder (MDD) is a debilitating and heterogeneous disorder with brain related changes. However, brain-related biomarkers to predict treatment outcomes on antidepressants have yet to be refined. Functional magnetic resonance imaging (fMRI) has been used to understand resting-state brain function, both regional interactions, (i.e., connectivity), and cerebral blood flow (CBF; perfusion). Resting-state functional connectivity (RSFC), as measured by blood-oxygenated-level dependent (BOLD) contrast imaging, and CBF, as measured by Arterial Spin Labeling, has been used to understand resting-state brain function and detect abnormalities. Abnormalities in connectivity and perfusion with in major functional networks (e.g., emotion and reward processing) have been detected in MDD, and could thus serve as a biomarker of treatment response. The present work aims to identify resting-state fMRI predictors of treatment response in MDD.

Method: As part of the Establishing Moderators/Biosignatures of Antidepressant Response in Clinical care study, a multi-site randomized placebo-controlled trial of antidepressant response in MDD, participants underwent neuroimaging at baseline, prior to starting study medication, including resting-state BOLD and ASL. Participants were randomized to either Sertraline (SERT) or Placebo (PBO) and treatment response, i.e., depression severity, was monitored for 8-weeks using the 17-item Hamilton Depression Rating Scale (HAMD-17). RSFC was computed for 265 participants (132 SERT, 133 PBO) using seeds in brain regions belonging to major functional networks impacted by MDD such as the amygdala (emotion), and the ventral striatum (reward). Relative CBF (rCBF) was calculated for 231 participants (114 SERT, 117 PBO). RSFC and rCBF data were entered into whole-brain, voxel-wise linear mixed effects models to identify brain regions in which resting-state fMRI levels moderate treatment response as measured by the HAMD-17. Number needed to treat to achieve remission was calculated to determine clinical effectiveness of moderators.

Results: RSFC moderators of treatment outcome (FDR $p<.05$) for the amygdala seed: 1) thalamus, and 2) middle frontal gyrus; and the ventral striatum seed: 1) middle temporal gyrus, 2) medial frontal gyrus, 3) middle frontal gyrus, 4) medial frontal gyrus and BA6, 5) superior temporal gyrus, and 6) medial frontal gyrus and caudate. The lowest number of participants

(2.75) to treatment was found when there was high connectivity between the amygdala (seed) and the thalamus. rCBF moderators of outcome were identified in the inferior, middle, and superior frontal gyri, inferior temporal gyrus, fusiform, parahippocampus, anterior cingulate and calcarine cortices, thalamus, and caudate. Number needed to treat to achieve remission on SERT for these regions were 2.64-7.25.
Conclusions: Resting-state fMRI predictors of antidepressant treatment response and their clinical effectiveness were identified in regions involved with reward and emotion processing in MDD. These brain regions have been implicated in the etiology of MDD, e.g. anhedonia and emotion dysregulation, and moderate treatment response. Data such as these aid the field of psychiatry in classifying and treating MDD beyond just clinically-derived symptom profiles, but rather augmented by pathophysiology-derived diagnostic and prognostic markers of illness and clinical response.

Learning Objectives

1. Using resting-state connectivity to predict antidepressant treatment response in Major Depressive Disorder.
2. Using cerebral blood perfusion to predict antidepressant treatment response in Major Depressive Disorder.

Literature References

1. Trivedi MH, McGrath PJ, Fava M, et al:. Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. J Psychiatr Res. 2016; 78:11-23.
2. Phillips ML, Chase HW, Sheline YI, et al: Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches. Am J Psychiatry. 2015; 172:124-138.

IT'S NOT JUST AUTISM: ASD AND ASSOCIATED PSYCHOPATHOLOGY AND COGNITIVE DYSFUNCTION*

Gagan Joshi, Massachusetts General Hospital

Overall Abstract: Autism spectrum disorder (ASD) is a lifelong developmental disorder associated with high morbidity and disability (Kogan, 2009) that is estimated to affect up to 2% of youth in the general population (Blumberg, 2013). While there is increased recognition of ASD in intellectually capable populations (Baird, 2006), such individuals often experience considerable functional deficits, many of which have been understudied. Among potential contributors to the morbidity in individuals with high functioning ASD (HF-ASD) are neuropsychological deficits and psychopathology.
Our first speaker presents findings from a study comparing the neuropsychological findings of adults with HF-ASD with two non-ASD groups, with and without ADHD, of similar age and sex. No differences in IQ were found, but subjects with HF-ASD were significantly more impaired than both comparison groups in processing speed, cognitive flexibility and sight words. These findings suggest that there may be specific neuropsychological correlates of HF-ASD that could have significant implications for identifying individuals at risk for ASD.
In addition to a number of studies documenting comorbid conditions being present in individuals with ASD, recent studies showed that symptoms of autism or autistic traits (ATs) appear in 20 to 30 percent of children with ADHD (Grzadzinski, 201; Kochhar, 2011;

Mulligan, 2009). Our second speaker presents on the prevalence of ATs in youth with ADHD. Youth with ADHD and healthy controls were compared on the presence of ATs. An ASD diagnosis was exclusionary, and assessments included measures of psychiatric, psychosocial, educational, and cognitive functioning. A positive AT profile was significantly overrepresented among ADHD children versus controls. Children with ADHD and ATs appeared to be more impaired and dysfunctional than children with ADHD only.

The third speaker discusses emotional dysregulation (ED) in youth with ASD. Youth with ASD were compared to youth with ADHD and healthy controls on the prevalence of the two profiles of ED in the Child Behavior Checklist (CBCL) (Achenbach, 1991). The majority of youth with ASD had positive CBCL-ED profile, which was significantly higher than in youth with ADHD. Similarly, the severe emotional dysregulation (SED) profile was significantly greater in youth with ASD than with ADHD. In the presence of the SED profile, ASD youth suffered from greater severity of autism, associated psychopathology, and psychosocial dysfunction.

Despite increased and extensive documentation of autistic traits and autism disorder, there has been limited success in the amelioration of deficits associated with an ASD diagnosis, suggesting more research on the biomarkers of ASD is needed. The fourth speaker presents findings on the glutamate (Glu) levels in the dorsal ACC (dACC) of ASD subjects with and without ED, and healthy controls (HCs). Glu concentrations in the dACC of 36 HF-ASD adolescents and age and sex matched HCs were measured using high field (4.0 Tesla) proton MRS. HF-ASD subjects were grouped based on CBCL subscale scores previously associated with deficits in emotional regulation. The Glu levels in the dACC of adolescents with HF-ASD were significantly higher than age and sex matched HCs, and ASD+ED subjects had significantly higher Glu levels than subjects with only ASD and HCs.

Learning Objectives

1. To inform on the cognitive correlates of ASD and the morbidity and dysfunction associated with autistic traits in psychiatrically referred population.
2. To discuss the burden of emotional dysregulation associated with ASD, and to present brain glutamate activity in the context of ASD and emotional dysregulation.

NEUROPSYCHOLOGICAL CORRELATES OF AUTISM SPECTRUM DISORDERS: A CONTROLLED STUDY OF ADULTS WITH HIGH FUNCTIONING ASD

Ronna Fried, MGH/Harvard Medical School

Individual Abstract: Objective: The main purpose of this study was to examine the neuropsychological underpinnings of High Functioning (IQ>80) Autism Spectrum Disorder (HF-ASD) attending to comorbidity with ADHD. ADHD is comorbid at a rate of 80% in ASD; thus, we compared the scores on a range of cognitive/neuropsychological tests of the adults with HF-ASD to adults with and without ADHD of similar age and sex.

Participants and Methods: Participants included 26 adults with HF-ASD, 52 adults with ADHD, and 52 Controls. All subjects were administered the following assessments: the Wechsler Abbreviated Scale of Intelligence, Processing speed and Working Memory subtests from the Wechsler Adult Intelligence Scale-IV, tests of executive functioning from the Delis Kaplan Executive Functioning System, the Test of Word Reading Efficiency, and the Wide Range Achievement Test in Math. For continuous outcome variables, a linear regression model was used; for binary outcome variables, a logistic regression was used. If the overall test of equality of groups showed that some groups differed from the others, then pairwise tests were carried out using Tukey adjustments.

Results: Two subjects from the ADHD and Control groups were matched to each ASD subject. Since SES was lower in the ASD group, all subsequent tests corrected for SES. There were no other significant differences in socio-demographic characteristics between groups. No differences in IQ were found among the groups. HF-ASD subjects were significantly more impaired than both comparison groups in processing speed, cognitive flexibility and sight words. HF-ASD subjects were more impaired than Controls in Working Memory, but not compared to ADHD subjects.
Conclusions: Our findings reveal very robust neuropsychological deficits in subjects with HF-ASD in comparisons with subjects with ADHD as well as Controls. The finding of a unique neuropsychological profile within HF-ASD could have significant implications for identifying individuals at risk for ASD in clinical settings, where the tests utilized in this study are commonly administered.

Learning Objectives

1. Our findings will show the possible differences between testing results for individuals with ASD plus ADHD vs. ADHD alone to reduce the number of cases of ASD initially misdiagnosed with ADHD as the only disorder.
2. Our results can help with the understanding of the neurobiology associated with rigid behavior in ASD and thus allow for better treatment planning.

Literature References

1. Willcut E, Sonuga-Barke EJ, Nigg JT, et al: Recent Developments in Neuropsychological Models of Childhood Psychiatric Disorders. Recent Adv Biol Psychiatry 2008; 24:195-226.
2. The Neuropsychology of Autism. Edited by Fein D. New York, Oxford University Press, 2011.

AUTISTIC TRAITS IN CHILDREN WITH AND WITHOUT ADHD

Joseph Biederman, Massachusetts General Hospital

Individual Abstract: Objective: To assess the implications of autistic traits (ATs) in ADHD youth without a diagnosis of autism.
Methods: Participants were youth with (N=242) and without (N=227), and controls without ADHD where a diagnosis of autism was exclusionary. Assessment included measures of psychiatric, psychosocial, educational, and cognitive functioning. Autistic traits (AT) were operationalized using the Withdrawn + Social + Thought Problems T-scores from the CBCL.
Results: A positive AT profile was significantly overrepresented among ADHD children vs. controls (18% vs. 0.87%, $p<0.01$). ADHD children with the AT profile were significantly more impaired than controls in psychopathology, interpersonal, school, family and cognitive domains.
Conclusions: A substantial minority of ADHD children manifests autistic traits (ATs) and those exhibiting ATs have greater severity of illness and dysfunction.

Learning Objectives

1. The audience will learn about the overlap between autistic traits and ADHD.
2. The audience will learn about the morbidity associated with autistic traits in youth with ADHD.

Literature References

1. Grzadzinski R, Di Martino A, Brady E, et al. Examining autistic traits in children with ADHD: Does the autism spectrum extend to ADHD? J Autism Dev Disord 2011; 41(9):1178-1191.
2. Kochhar P, Batty MJ, Liddle EB, et al. Autistic spectrum disorder traits in children with attention deficit hyperactivity disorder. Child Care Health Dev 2011; 37(1):103-110.

HIGH RISK FOR SEVERE EMOTIONAL DYSREGULATION IN PSYCHIATRICALLY REFERRED YOUTH WITH AUTISM SPECTRUM DISORDER: A CONTROLLED STUDY

Janet Wozniak, Harvard Medical School, Massachusetts General Hospital

Individual Abstract: Background: Prevalence of ASD is considerably higher in psychiatrically referred populations of youth, ranging from 2-14%. Psychiatric referrals of children with ASD are frequently driven by emotional and behavioral problems. Emotional dysregulation (ED) is characterized by poor self-regulation including symptoms of low frustration tolerance, impatience, quickness to anger, and emotional reactivity. Within the context of ASD, researchers have defined ED in distinctive ways for assessing deficits in regulation of emotions. We have operationalized different levels of ED using a unique profile of the Child Behavior Checklist (CBCL) (Achenbach, 1991) consisting of elevated scores of the Anxiety/Depression, Aggression, and Attention subscales. The ED profile on the CBCL (CBCL-ED) can help identify moderate [≥1SD and <2SD; Deficient Emotional Self-Regulation (DESR)] or severe [≥2SDs; Severe Emotional Dysregulation profile (SED)] levels of ED in children with emotional and behavioral difficulties. Although deficits in regulation of emotions have been documented in children with ASD the prevalence of ED based on the varying severity levels of CBCL-ED profile and whether the two sub-forms of ED are clinically helpful in distinguishing distinct levels of deficits in children with ASD remains unclear. Considering the empirical nature of the CBCL, its excellent psychometric properties, and its ease of implementation, documenting the magnitude and severity of ED per CBCL operationalized criteria in ASD populations remains an area of very high clinical importance. The knowledge derived from this work could translate into improved recognition and therapeutics for ASD children at risk for differently compromised courses and outcomes.
Objective: The main aim of the present study is to: 1) examine the prevalence of the two CBCL-based ED profiles in ASD; and 2) investigate whether the two severity levels of CBCL profiles for ED can help distinguish clinically distinct levels of deficits in ASD. We hypothesized that the two CBCL-ED profiles in youth with ASD would identify differentiating patterns of clinical correlates.
Methods: ASD youth (N=123) were compared to youth with attention-deficit/hyperactivity disorder (ADHD) and healthy controls. We compared the prevalence of the two CBCL-ED profiles in psychiatrically referred population of youth with ASD to those with ADHD and to healthy controls (HC). Furthermore, we directly compared the demographic, psychopathological, and functional correlates associated with the two CBCL-ED profiles in youth with ASD.
Results: The majority of psychiatrically referred youth with ASD had positive CBCL-ED profile that was significantly higher than in youth with ADHD (82% vs. 53%; $p<0.001$). The SED profile was significantly greater in ASD youth than ADHD (44% vs. 15%; $p<0.001$). In the presence of SED profile ASD youth suffered from greater severity of autism, associated psychopathology, and psychosocial dysfunction.

Conclusions: There was greater than expected prevalence of SED in psychiatrically referred youth with ASD that identifies distinct clinical correlates associated with severe morbidity and dysfunction.

Learning Objectives

1. To educate the audience regarding the prevalence of the two CBCL-based emotional dysregulation profiles in ASD.
2. To examine whether the two severity levels of CBCL profiles for ED can help distinguish clinically distinct levels of deficits in ASD.

Literature References

1. Mazefsky, CA, Borue, X, Day, TN, et al: Emotion regulation patterns in adolescents with high-functioning autism spectrum disorder: comparison to typically developing adolescents and association with psychiatric symptoms. Autism Res 2014; 7:344-354.
2. Samson, AC, Phillips, JM, Parker, KJ, et al: Emotion dysregulation and the core features of autism spectrum disorder. J Autism Dev Disord 2014; 44:1766-1772.

MR SPECTROSCOPIC GLUTAMATE ACTIVITY IN HIGH-FUNCTIONING AUTISM SPECTRUM DISORDER ADOLESCENTS WITH AND WITHOUT EMOTIONAL DYSREGULATION

Gagan Joshi, Massachusetts General Hospital

Individual Abstract: Background: Previous research has noted significantly high glutamate (Glu) levels in the anterior cingulate cortex (ACC) of high-functioning autism spectrum disorder (HF-ASD) youth (Joshi et al. 2012), as well as correlations between Glu levels in the ACC and severity of Emotional Dysregulation (ED) in youth (Wozniak et al. 2012). This study examines the Glu levels in the dorsal ACC (dACC) of ASD subjects with and without ED, and healthy controls (HCs).
Objectives: To assess the Magnetic Resonance Spectroscopic Glutamate activity in the dACC of HF-ASD adolescents with and without emotional dysregulation (ED).
Methods: We measured Glu concentrations in the dACC of 36 HF-ASD adolescents (aged 8-18 years) and age and sex matched HCs, using high field (4.0 Tesla) proton MRS. HF-ASD subjects were grouped based on CBCL subscale scores previously associated with deficits in emotional regulation (N=29). ASD subjects with ED (>180) were further separated into those with severe emotional dysregulation (SED) (>210) (N=11) and deficient emotional self-regulation (DESR) (<210, >180) (N=18).
Results: The Glu levels in the dACC of adolescents with HF-ASD were significantly higher than age and sex matched HCs (p=0.005). ASD+ED subjects had significantly higher Glu levels than subjects with only ASD and HCs (p=0.006). Severity of ASD, as measured by the Social-Responsiveness-Scale (SRS), was positively correlated (p=0.057) with Glu levels in the dACC. Subjects with ASD+SED had the strongest positive correlation (p=0.001) between severity of ED and Glu levels in the dACC.
Conclusions: These results suggest that glutamatergic dysregulation in the dACC could be a useful biomarker of ASD and ED in adolescents.

Learning Objectives

1. To gain insight into Glutamate activity in the dorsal ACC of adolescents with high-functioning ASD.

2. To assess Glutamate concentrations in the dorsal ACC of high-functioning ASD adolescents with and without emotional dysregulation.

Literature References

1. Joshi G, Biederman J, Wozniak J, et al: Magnetic resonance spectroscopy study of the glutamatergic system in adolescent males with high-functioning autistic disorder: a pilot study at 4T. Eur Arch Psychiatry Clin Neurosci 2012; 263:379-84.
2. Wozniak, J, Gönenç A, Biederman J, et al: A magnetic resonance spectroscopy study of the anterior cingulate cortex in youth with emotional dysregulation. Isr J Psychiatry Relat Sci 2012; 49:62-9.

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

THE OPIOID EPIDEMIC: CRISIS AND SOLUTIONS*
Phil Skolnick, Opiant Pharmaceuticals, Inc.

Overall Abstract: The abuse of prescription opioids and dramatic increase in the availability of illicit opioids, including heroin and fentanyl, has reached epidemic proportions. The leading edge of this 'opioid epidemic' is the dramatic spike in overdose deaths (estimated at more than 53,000 in 2016.). However, increases in both the reported cases of neonatal abstinence syndrome and ER visits related to opioid overdose (in excess of 1.5 million in 2015), as well as a resurgence in infectious diseases (HIV, Hepatitis C) related to injection drug use are all less publicized but serious consequences of this epidemic. Three principal therapeutic approaches can be used to quell this epidemic: a) using effective agents to treat overdose; b) increasing both the availability and efficacy of medication-assisted treatments (MATs); and c) developing effective alternatives to traditional opioids for the treatment of acute and chronic pain. This panel will provide an overview of each of these therapeutic approaches. Roger Crystal will describe the rapidly evolving nature of opioid overdose, with fatalities attributed to 'synthetics' (e.g. fentanyl) now surpassing both prescription opioids and heroin. He will discuss the use of naloxone (currently the only FDA-approved medication to treat opioid overdose) as a rescue medication, and the potential for developing alternatives. Sublingual and buccal buprenorphine has been a mainstay of MATs for opioid use disorders (OUDs). Kate Beebe will discuss the development of new, long term, continuous delivery buprenorphine formulations (implants and injections) that produce therapeutic blood levels ranging from one week to six months. The concept of developing vaccines to target abused opioids (e.g., heroin, oxycodone, fentanyl) raises the possibility that a patient can be immunized against these compounds while receiving another MAT such as buprenorphine, methadone, or naltrexone. Gary Matyas will describe the challenges of raising antibodies against a small molecule (opioid). Alternatives to traditional opioids that retain high analgesic efficacy but lack some of the properties (e.g. euphoria, development of tolerance and physical dependence) that increase the likelihood of developing an OUD is a longer-term strategy that may be the most promising solution to end the opioid epidemic. Laura Bohn will discuss the development of 'biased' mu receptor agonists that signal primarily through G-protein-coupled receptor pathways. In preclinical models, these biased agonists appear to retain the analgesic properties of traditional opioids but lack some of the pharmacological effects that lead to misuse and abuse.

Learning Objectives

1. Understand the use and limitations of rescue medications to treat opioid overdose.
2. Understand new and emerging medication assisted treatment (MAT) approaches for opioid use disorders, including novel formulations of buprenorphine and vaccines directed against opioids.

OVERDOSE: THE LEADING EDGE OF THE OPIOID EPIDEMIC
Roger Crystal, Opiant Pharmaceuticals, Inc.

Individual Abstract: In 2016, more than 53,000 deaths were attributed to opioid overdose in the United States. While there has been a steady increase in opioid overdose deaths since the late 1990s, during the past 5 years there has been a rapid and remarkable evolution in the nature of these opioid related fatalities. Thus, in 2013, deaths attributed to illicit opioids surpassed prescription opioid overdose deaths; in 2016, illicit opioids were responsible for more than two thirds of these fatalities. This trend has been catalyzed by the ready availability and increased misuse of illicit 'synthetics' – principally fentanyl and its derivatives. Fentanyl is inexpensive and relatively simple to synthesize, obviating the need to grow and cultivate opium poppies. It is about 50-fold more potent than heroin, making it easy to transport. Fentanyl is also readily derivatized, and a simple analog, carfentanil, is about 5,000-fold more potent than heroin. Its potency, speed of onset, and long half-life all contribute to fentanyl becoming the leading cause of overdose deaths in the United States. The opioid antagonist naloxone is currently the only available means of rapidly and effectively reversing opioid overdose. While first approved for parenteral administration more than 40 years ago, in response to the rise in opioid overdose emergencies, multiple naloxone products are now available to first responders (e.g. police, EMS), including an intranasal formulation that can be used without prior training and produces blood levels as rapidly as an intramuscular injection. I will describe these naloxone products and discuss their efficacy as rescue medications as more individuals are exposed to a spectrum of high and ultra-high potency opioids.

Learning Objectives
1. Gain an understanding of the rapidly changing nature of opioid overdose (from prescription opioids to "synthetics" such as fentanyl).
2. Understand the role, use, and types of naloxone products currently available to treat opioid overdose.

Literature References

1. Krieter P, Chiang N, Gyaw S, et al: Pharmacokinetic properties and human use characteristics of an FDA approved intranasal naloxone product for the treatment of opioid overdose. J Clin Pharmacol 2016; 56:1243-1253
2. Rudd RA, Seth P, David F, et al.: Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:1445–1452

EMERGING MEDICATIONS FOR OPIOID USE DISORDER
Genie Bailey, Brown University and Stanley Street Treatment and Resources, Inc

Individual Abstract: Addiction to opioids, and the morbidity and mortality associated with this chronic, neurobiological disease, has been recently recognized as a national health emergency, with parallels drawn between the HIV/Aids crisis of the 1980s, and this current public health crisis. For the past decade, the mainstay of medication assisted treatment for opioid use disorder has been daily oral (sublingual) buprenorphine. Now, more than ever, new

and better treatment options are needed to improve patient engagement-in and adherence to therapy, to reduce the risk of diversion and misuse of oral formulations, and to mitigate unintended exposure to vulnerable populations such as children and the elderly.
This presentation will review the efficacy and safety of emerging, long-term formulations and delivery systems for buprenorphine, including 6-month buprenorphine implants, weekly and monthly buprenorphine injections, as well as monthly injections and 6-month implants of opioid antagonists for the prevention of opioid relapse and overdose.

Learning Objectives

1. To understand currently approved treatment options for opioid use disorder.
2. To understand emerging treatment options for the prevention of opioid relapse and overdose.

Literature References

1. Rosenthal, R.N., Ling, W., Casadonte, P., Vocci, F., Bailey, G.L., Kampman, K.M., Patkar, A., Chavoustie, S., Blasey, C., Sigmon, S.,Beebe, K.L., (2013) Buprenorphine Implants for Treatment of Opioid Dependence: Randomized Comparison to Placebo and Sublingual Buprenorphine/Naloxone. Addiction. 108 (12); 2141-9.
2. Rosenthal, R.N., Lofwall, M.R., Kim, S., Chen, M. Beebe, K.L., Vocci, F. (2016) Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults with Opioid Dependence Treated with Sublingual Buprenorphine; A Randomized Clinical Trial. JAMA. 316(3): 282-290.

DEVELOPMENT OF A HEROIN VACCINE THAT INDUCES ANTIBODIES THAT ALSO BIND TO ABUSED PRESCRIPTION OPIOIDS

Gary Matyas, Walter Reed Army Institute of Research

Individual Abstract: One novel approach to the treatment of drug abuse is to develop vaccines that prevent the pharmacological effects of the drug. Although the vaccines do not reduce the physical dependence of the drug in addicts, vaccines will prevent the drug-induced euphoria. They may also be practically important in preventing relapse and drug overdose by blocking or muting the pharmacological effects of the drug. The mechanism of protection of vaccines is to induce antibodies that bind to the drug, sequester it in the blood and prevent it from the crossing the blood-brain barrier. However, the development of vaccines to drugs of abuse presents a number of problems. The drugs are too small to be immunogenic when injected and therefore, surrogate drug haptens must be coupled to a carrier to induce antibody responses to the drug. Both high titer antibodies and high affinity antibodies that have a long duration are required. The vaccine will need a potent adjuvant to induce the high titer and long duration antibodies.
Vaccine development against heroin is particularly difficult because heroin is rapidly metabolized to 6-acetylmorphine and morphine after injection. Consequently, a vaccine for heroin must induce antibodies that bind not only to heroin, but also its metabolites. Two heroin haptens, MorHap and 6-AmHap, were tested as antigens for a candidate heroin vaccine. MorHap is a morphine analog containing the functional group used for coupling at the 6 hydroxyl position. 6-AmHap is a heroin analog in which the amide group is substituted for the acetyl group at the 6 position. The functional coupling group in 6-AmHap is at the 3 position. The haptens were conjugated to tetanus toxoid (TT) and mixed with Army Liposome Formulation (liposomes containing monophosphoryl lipid A) as an adjuvant. Similar to the previously reported studies on MorHap-TT in mice, the 6-AmHap-TT conjugate vaccine

induced high anti-hapten IgG levels that reduced heroin-induced antinociception and locomotive behavioral changes following repeated subcutaneous and intravenous challenges in both mice and rats. 6-AmHap-TT vaccination completely prevented the heroin-induced loss of thermal sensitivity in rats in the thermal place preference test. As measured by competition ELISA, 6-AmHap-induced antibodies had significantly higher affinities than MorHap-induced antibodies to heroin and all its active metabolites. In addition, 6-AmHap-induced antibodies cross-reacted with other abused prescription opioids, including hydrocodone, oxycodone, hydromorphone, oxymorphone and codeine. Using equilibrium dialysis with UPLC-MS/MS detection, the Kd of the 6-AmHap-induced antibodies was approximately 0.5 nM to 6-acetylmorphine and morphine as compared to 2-3 nM for the MorHap-induced antibodies. 6-AmHap-TT was further tested in mice, which had a reduced heroin-induced hyperlocomotion as compared to unvaccinated animals when challenged with a high heroin dose of 50 mg/kg. Overall, these data suggest that the 6-AmHap hapten is an ideal hapten candidate for testing in a clinical vaccine trial as a therapeutic for heroin and opioid abuse.

Learning Objectives

1. To understand how vaccines to substances of abuse function.
2. A vaccine to heroin and other abused prescription opioids can prevent overdose and block the effects of the opioids.

Literature References

1. Jalah R, Torres OB, Mayorov AV, Li F, Antoline JF, Jacobson AE, Rice KC, Deschamps JR, Beck Z, Alving CR, Matyas GR. Efficacy, but not antibody titer or affinity, of a heroin hapten conjugate vaccine correlates with increasing hapten densities on tetanus toxoid, but not on CRM197 carriers. Bioconjug Chem. 2015;26:1041-1053.
2. Torres OB, Matyas GR, Rao M, Peachman KK, Jalah R, Beck Z, Michael NL, Rice KC, Jacobson AE, Alving CR. Heroin-HIV-1 (H2) vaccine: induction of dual immunologic effects with a heroin hapten-conjugate and an HIV-1 envelope V2 peptide with liposomal lipid A as an adjuvant. npj Vaccines. 2017;2:13.

USING MU OPIOID RECEPTOR BIASED AGONISM TO REFINE OPIOID ANALGESICS

Laura Bohn, The Scripps Research Institute

Individual Abstract: Biased agonism describes a context wherein a ligand has the ability to preferentially promote receptor signaling towards one pathway over another as compared to a reference agonist at the same receptor. Extensive research using mice lacking the scaffolding protein, beta-arrestin2, suggests that agonists that active the mu opioid receptor to promote G protein signaling and avoid beta-arrestin2 recruitment may provide a way to uncouple opioid analgesia and certain side effects. In this presentation, we will show examples of such agonists, differing in their degree of bias for promoting G protein signaling over beta-arrestin2 recruitment and how that translates to preserving analgesic properties while avoiding respiratory suppression acutely. Chronic treatment studies, with care taken to maintain steady state pharmacokinetics, are also presented for the assessment of antinociceptive tolerance. Overall, these studies support the rationale for the development of G protein biased MOR agonists as a means to preserve analgesic efficacy and prevent respiratory suppression and tolerance.

Funding: NIDA R01DA038964, and R01DA033073.

Learning Objectives

1. Understand the concept of biased agonism at GPCRs, particularly opioid receptors.
2. Understand that the degree of bias between two signaling assays correlates with the degree of separation of the therapeutic window.

Literature References

1. Schmid CL, Kennedy NM, Ross NC, Lovell KM, Yue Z, Morgenweck J, Cameron MD, Bannister MD, Bohn LM (2017) Bias factor and therapeutic window correlate to predict safer opioid analgesics. Cell. In press (Nov 16, 2017).
2. Zhou L and Bohn LM. (2014) Functional Selectivity of GPCR Signaling in Animals. Current Opinion in Cell Biology (special edition, M von Zastrow and J Benovic, Editors), 27:102-8. PMID: 24680435.

PHARMACODYNAMIC AND COGNITIVE EVALUATION OF CNS DRUGS IN CLINICAL TRIALS OF CANNABIS AND DRIVING IMPAIRMENT

Beatrice Setnik, Syneos Health

Overall Abstract: Evaluating the impact of drugs on perceptions and cognitive abilities is an integral component of abuse and dependence potential, which informs the overall safety, appropriate dosing, and scheduling of a drug. Methodological approaches to assess drug discrimination and physical dependence continue to evolve and thus, require careful evaluation of both preclinical animal studies and clinical data. In this context, our growing scientific understanding of the activity and therapeutic potential of psychoactive agents, such as cannabis (ie, tetrahydrocannabinol - THC, cannabinoid - CBD, and other terpenes) depends on the ability to undertake innovative research on the efficacy of different strains. The ubiquitous use of prescription and non-prescription drugs presents a major public safety concern since psychoactive substances may diminish the awareness of drug-related impairments, the skills required for safe driving, and may increase motor vehicle accident (MVA) risks. Cannabis has recently been shown to contribute to MVA risks (Asbridge et al, 2014). Other prescription drugs including benzodiazepines have also been shown to negatively impact driving skills (Dubois et al, 2008).

In the clinical setting, the guidelines for the assessment of human abuse potential (Food and Drug Administration, 2017) provide additional information regarding studies of cognition and performance to evaluate a drug's impairing effects, the clinical evaluation of physical dependence, design considerations, and novel insights into expected statistical analyses. A draft regulatory guidance (Food and Drug Administration, 2015) outlines a new set of criteria regarding the impact of drugs on the CNS functions necessary for the ability to operate a motor vehicle. In contrast, the regulatory landscape surrounding medicinal cannabis presents as a tangled and contradictory web of regulations among FDA (Food and Drug Administration, 2016), DEA, state-based approaches, and patient and recreational use advocates and is nearly unrecognizable as compared to all other psychotropic compounds. Thus, adopting a cohesive conceptual framework that incorporates data from pharmacodynamic, pharmacokinetic, and adverse events can collectively inform on the impairing potential of psychotropic compounds. Evaluation criteria of the potential risks of driving impairments, including secondary or unforeseen effects applying to CNS-acting agents will be explored. Study populations must be carefully considered, especially when it may be impossible to conduct a study in the intended

patient population because of important safety concerns associated with the discontinuation of a drug. Study endpoints may vary by drug class, type, and dose range. For lengthier trials, practical considerations of the feasibility of confined stays have to be addressed. In the case of a drug's effect on driving ability the risk of actual motor vehicle accidents cannot be used as an endpoint as this would be unethical. 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 cannabis and the driving impairing potential of psychotropic compounds. Moving forward, various evolving regulatory challenges will need to be addressed.

Learning Objectives

1. Gain further understanding of the cannabis regulatory landscape and the impact of psychoactive drugs on driving.
2. Understand the clinical methods and outcome measures needed to sensitively evaluate the subjective and objective effects of CNS active drugs across multiple drug development trials in the clinical setting.

A GPS FOR THC: LOOKING FOR A SCIENCE-BASED REGULATORY FRAMEWORK FOR CANNABINOID MEDICINES WHEN WE CAN'T DECIDE WHICH WAY IS UP

Michael Hufford, Pinney Associates

Individual Abstract: The regulatory landscape surrounding medicinal cannabis is nearly unrecognizable as compared to any other class of psychotropic compounds. There is a chasm between the evolving scientific understanding of the activity and therapeutic potential of tetrahydrocannabinol (THC), cannabinoid (CBD) and other terpenes on the one hand, and the tangled and contradictory web of regulations among US Food and Drug Administration (FDA), Drug Enforcement Agency (DEA), state-based approaches, and patient and recreational use advocates on the other hand. Currently, there is active scientific disagreement on almost all aspects of cannabinoid medicines. For example, The National Academic of Sciences (2017) recently concluded that "There is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults", whereas the DEA (2016) concluded that "…there are no adequate or well-controlled studies that prove marijuana's efficacy." Similar contradictions exist around the role of cannabis in alleviating (Boehnke et al., 2016) versus exacerbating (Olfson et al., 2017) opioid dependence. Contradictory conclusions drawn from the same scientific literature mirror a broader disconnect among federal and state-based approaches to the regulation of products containing THC and CBD. For example, a medicinal THC-based product prescribed by a physician in one state can lead to seizure and arrest of a patient with that product in another state. Within this web of contradictory scientific conclusions and regulations, researchers and clinicians must decide what data are likely to be compelling to regulators regarding not only the safety and efficacy, but also the abuse liability of novel drugs that are seeking to use the unique pharmacology of THC- and CBD-like compounds to treat neuropsychiatric illnesses.

Learning Objectives

1. Gain further understanding of the cannabis regulatory landscape and its impact on research regarding THC- and CBD-like compounds in clinical development.

2. Understand how existing regulatory frameworks for other psychotropic drugs, including a systematic review of their abuse liability using an 8-factor analysis, may aid researchers in their development of novel cannabinoid-like drugs.

Literature References

1. Boehnke KF, Litinas E, Clauw DJ: Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain 2016; 17:739–744.
2. Olfson M, Wall, MM, Liu, S-M, Blanco, C. Cannabis use and risk of prescription opioid use disorder in the United States. AJP in Advance (doi: 10.1176/appi.ajp.2017.17040413).

CANNABINOIDS: A DRIVING FORCE - EVALUATING METHODOLOGICAL AND CLINICAL CHALLENGES TO TESTING ABUSE POTENTIAL AND DRIVING IMPAIRMENT

Talar Hopyan, Syneos Health

Individual Abstract: The psychoactive effects of one of the principal components of cannabis, THC, has been well characterized. However, unlike THC, cannabidiol (CBD), is thought to have non-psychoactive effects. CBD is reported to have analgesic and anxiolytic properties.
The evolving regulatory landscape and the opioid epidemic has many patients and caregivers to seek out cannabinoids as an alternative option for treatment of unmet medical needs, especially in the area of pain.
Individual cannabinoids have been approved for various indications (e.g., appetite stimulants), however, many more compounds are currently under clinical investigation, including for acute and chronic pain. Understanding the safety and abuse potential of these compounds is integral to clinical development of cannabinoids. In addition, evaluating the potential for risk with respect to cannabinoids and driving impairment is also critical especially given the new FDA Guidance on driving and drug development (2017). Driving a motor vehicle is a series of complex psychomotor tasks that most people undertake on a regular basis. Cannabis, has long been suspected of contributing to motor vehicle collisions (MVCs), but clear evidence of that contribution has been relatively recent. The purpose of this talk is to discuss the clinical trial methodology and challenges to testing the abuse and dependence potential as well as safety of cannabinoids and the regulatory pathway with regards to the FDA abuse potential assessment guidance (2017). The presentation will cover data from the literature on cannabinoid abuse and dependence potential as well as evaluating driving impairment.

Learning Objectives

1. Understand regulatory requirements for human abuse potential and driving simulator studies with THC and CBD.
2. Evaluate and understand the clinical methodology for human abuse potential and driving simulator studies with THC and CBD.

Literature References

1. FDA Assessment of Abuse Potential of Drugs Guidance for Industry (2017).
2. FDA Evaluating Drug Effects on the Ability to Operate a Motor Vehicle Guidance for Industry (2017).

SELECTING SUBJECTIVE BEHAVIORAL AND OBJECTIVE COGNITIVE MEASURES FOR CLINICAL TRIALS OF CANNABIS AND DRIVING IMPAIRMENT

Denise Milovan, INC Research

Individual Abstract: The potential impact of medications on cognitive abilities has been progressively recognized as a key safety aspect of clinical drug development. In November 2017, FDA issued a final industry guidance regarding the evaluation of drug effects on the ability to operate a motor vehicle (1), which emphasizes the importance of undertaking early testing of potential CNS-impairing effects using sensitive psychomotor and neuropsychological measures, as well as subjective reports. An effective drug development program should consider how cognition will be assessed, how to interpret the magnitude of identified effects, and how the strength of the correlation between subjective and objective impairment can best inform the potentially impairing properties of the pharmacological agent under study.

Cannabis intoxication has been shown to result in performance impairments across a wide range of neurocognitive domains including attention, executive function, impulse control, and psychomotor speed, irrespective of cannabis use history (2). Given the rapid changes in policy, the increasingly accepting public perception toward cannabis use, and the conclusive or moderate scientific evidence supporting the use of cannabis or cannabinoids for a variety of therapeutic indications (e.g., treatment of chronic pain in adults, antiemetic effects for chemotherapy-induced nausea and vomiting, improving spasticity symptoms in multiple sclerosis, improving short-term sleep outcomes), the ability to adequately and prospectively characterize potential cognitive deficits in a variety of patient populations and age groups may prove critical for the development of an evidence-based policy and legislation directed at drugs and driving.

The regulatory expectation for early clinical testing of CNS effects to employ objective cognitive tests of reaction time, divided attention, selective attention, memory, executive function, and psychomotor processing speed has been explicitly outlined in several FDA guidance documents. Thus, evaluating cognitive abilities, motor skills, and mood data is expected to improve the understanding of the safety profile of pharmacological agents, aid in the clinical decision-making process, and reduce the uncertainty regarding the potential cognitive impact once a drug is marketed. Reliance on sensitive, standardized cognitive measures that are resilient to practice effects and incorporate multiple levels of difficulty for the detection of cognitive impairment across the full ability span is ideal. The use of relevant subjective measures of the drug effects (e.g., visual analogue scales) is expected to contribute important information regarding the socially acceptable magnitude of impairments.

Learning Objectives

1. Practical considerations when selecting pharmacodynamic measures to evaluate the behavioral and cognitive effects of psychoactive substances, as well as safe driving skills.
2. Balancing selection of measures against treatment compliance and study feasibility.

Literature References

1. Food and Drug Administration (FDA). (2017). Evaluating Drug Effects on the Ability to Operate a Motor Vehicle. 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.
2. Ramaekers, J., van Wel, J., Spronk, D., Toennes, S., Kuypers, K., Theunissen, E., & Verkes, R. (2016). Cannabis and tolerance: acute drug impairment as a function of cannabis use history. Scientific Reports, 6(1), 26843.

EARLY-PHASE TRIALS OF NOVEL INTERVENTIONS FOR TREATMENT-RESISTANT DEPRESSION

Brian Mickey, University of Utah School of Medicine

Overall Abstract: Depression strikes 15 million individuals annually in the US alone, about 30% of whom do not respond to optimized treatment with conventional antidepressant medications. There is a critical need to develop novel antidepressant interventions.
This panel will present promising findings from recent early-phase trials of novel or repurposed agents that could help to meet this critical need. In each case, the agent discussed has proposed mechanisms of action that differ from those of conventional antidepressant medications. Open-label studies and ongoing or planned randomized trials will be presented.
Recent studies suggest efficacy of four unconventional agents for treatment-resistant depression. Dr. Carhart-Harris will present studies of psilocybin, a mushroom-derived psychedelic drug, administered with psychological support. Dr. Kious will discuss augmentation with creatine, a key intermediate in energy metabolism, and 5-hydroxytryptophan, a serotonin precursor. Dr. Murrough will share results from a trial of dextromethorphan, a cough suppressant with NMDA antagonist activity, and two other mechanistically novel agents. Dr. Mickey will present data supporting the tolerability and efficacy of propofol, a unique general anesthetic drug, for treatment-resistant depression.
Dr. Rapaport will guide discussion of the implications and limitations of these findings. Future investigations may be warranted to rigorously test the unconventional agents discussed here. Mechanistic studies of these agents could reveal novel therapeutic targets or alternative conceptualizations of treatment-resistant depression. Ultimately, the heterogeneous causes of depression will likely demand diverse interventions with distinct mechanisms of action.

Learning Objectives

1. To understand the significance of treatment-resistant depression and the critical need for novel antidepressants.
2. To become familiar with some unconventional agents currently being studied for their antidepressant effects.

PSILOCYBIN FOR MAJOR DEPRESSIVE DISORDER

Robin Carhart-Harris, Imperial College London

Individual Abstract: Psilocybin is a serotonin receptor agonist that has an ancient and modern history of therapeutic use. Recent work has supported the safety and efficacy of psilocybin for treating symptoms of anxiety and depression, including an open-label feasibility study from our team. This presentation will summarise clinical and fMRI results from this trial plus preliminary observations from a subsequent double-blind randomised controlled trial, comparing changes in depression and imaging outcomes after a single dose of psilocybin versus 6 weeks of daily escitalopram for major depressive disorder. This work promises to develop a

novel treatment modality for major depression that may revolutionise how we view and treat this common, debilitating and costly disorder.

Learning Objectives

1. Understand evidence base for psychedelics in psychiatry.
2. Understand pharmacology of psychedelics.

Literature References

1. Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, Kaelen M, Giribaldi B, Bloomfield M, Pilling S, Rickard JA, Forbes B, Feilding A, Taylor D, Curran HV, Nutt DJ (2017) Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl). 2017 doi: 10.1007/s00213-017-4771-x.
2. Carhart-Harris RL, Goodwin GM (2017) The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. Neuropsychopharmacology. 42(11):2105-2113. doi: 10.1038/npp.2017.84.

CLINICAL TRIALS OF 5-HYDROXYTRYPTOPHAN AND CREATINE MONOHYDRATE FOR SSRI OR SNRI AUGMENTATION IN TREATMENT RESISTANT DEPRESSION IN WOMEN

Brent Kious, University of Utah

Individual Abstract: Major depressive disorder is a complex syndrome resulting from endogenous and environmental factors. Altitude of residence appears to be an independent risk factor for depression, and is also associated with suicide. Altitude could affect such outcomes because increased altitude is associated with reduced atmospheric pressure and relative hypoxia. Chronic hypoxia could affect several pathways associated with depression. Hypoxia can impair serotonin synthesis by impeding the activity of tryptophan hydroxylase 2, which converts dietary tryptophan to 5-hydroxytryptophan (5-HTP). Women may be more vulnerable to this process, as rates of serotonin synthesis in women are lower than in men. Serotonin deficiency due to hypoxia could be corrected by administration of 5-HTP, which has previously been used as an antidepressant.

Depression is also associated with alterations in brain bioenergetics. The creatine kinase reaction mediates the production of adenosine triphosphate (ATP) from adenosine diphosphate and phosphocreatine (PCr). This reaction is important for the rapid production of ATP in metabolically active neurons. Alterations in the efficiency of the reaction could produce neuronal dysfunction, leading to depression. Phosphorus magnetic resonance spectroscopy (31P-MRS) shows reduced total nucleotide triphosphate concentrations and higher PCr concentrations in depressed adults than in healthy volunteers. Intriguingly, this pattern is also more common in women. Dysfunction in the creatine kinase pathway could be ameliorated by creatine monohydrate, which has demonstrated adjunctive antidepressant efficacy in other trials.

We hypothesized that augmentation of conventional antidepressants with creatine monohydrate and 5-HTP could correct deficits in serotonin synthesis and the creatine kinase pathway associated with depression, increasing antidepressant response in a synergistic fashion. I first present data from an 8-week open-label study of combined creatine and 5-HTP for SSRI/SNRI augmentation in 15 women. In that study, mean Hamilton Depression Rating Scale (HAM-D) scores declined from 18.9 + 2.5 at the pretreatment visits to 7.5 + 4.4 ($p <$

0.00001), a decrease of 60%. The treatment was well tolerated with no serious adverse events. I also present data from an ongoing placebo-controlled study incorporating resting state functional connectivity and 31P-MRS to assess neuroimaging markers of depression and antidepressant response. To date, results from 6 subjects suggest improvements in HAM-D scores over 8 weeks. Subjects also demonstrated a trend toward increased frontal PCr levels. In a logistic regression analysis, the correlation between HAM-D levels and PCr levels across both baseline and treatment assessments was negative (ß = -0.0018) and borderline significant (p = 0.052). We also demonstrated measurable changes in connectivity across the 6 subjects, involving the bilateral pregenual and subgenual anterior cingulate cortex (t~2.2). These regions are implicated in the pathogenesis of depression. Together, these data suggest that combination treatment with adjunctive 5-HTP and creatine is a promising approach to the management of depression and likely to produce anticipated changes in brain levels of high energy phosphate and frontal connectivity that are associated with clinical response.

Learning Objectives

1. Describe the possible mechanisms by which relative hypoxia could contribute to depression.
2. Discuss the potential contributions of 5-hydroxytryptophan and creatine monohydrate to the management of depression that has responded poorly to SSRIs or SNRIs.

Literature References

1. Young SN. Elevated incidence of suicide in people living at altitude, smokers and patients with chronic obstructive pulmonary disease and asthma: possible role of hypoxia causing decreased serotonin synthesis. Journal of Psychiatry and Neuroscience. 2013;38:423-426.
2. Kious BM, Sabic H, Sung YH, Kondo DG, Renshaw P. An Open-Label Pilot Study of Combined Augmentation With Creatine Monohydrate and 5-Hydroxytryptophan for Selective Serotonin Reuptake Inhibitor- or Serotonin-Norepinephrine Reuptake Inhibitor-Resistant Depression in Adult Women. J Clin Psychopharmacol. 2017;37:578-583.

ENHANCING NEUROPLASTICITY AND CELLULAR RESILIENCE AS NOVEL PHARMACOLOGICAL APPROACHES TO TREATMENT-RESISTANT DEPRESSION

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Background: Depression is a leading cause of disability worldwide. Major advances in basic neuroscience are providing new insights into mechanisms of depression and related disorders, and providing new targets for novel therapeutic discovery. This talk will review new and unpublished data from proof of concept (POC) clinical trials testing novel molecular approaches to enhancing neuroplasticity and cellular resilience in patients with mood disorders. Clinical and biological data from trials of the following agents will be reviewed: (1) dextromethorphan/quinidine (DM/Q), (2) ezogabine, and (3) minocycline. DM/Q engages glutamate NMDA receptors and sigma-1 receptors to trigger adaptive cellular changes hypothesized to underlie potential antidepressant effects in treatment-resistant depression (TRD). Ezogabine is a first-in-class neural KCNQ channel opener that demonstrates antidepressant activity in rodent models via normalization of stress-induced hyperactivity within the ventral vegmental (VTA)-nucleus accumbens (NAc) reward pathway.

Finally, minocycline is a tetracycline analog found to have multiple cellular effects that converge on neuroprotective pathways relevant to the putative pathophysiology of mood disorders.
Methods: For the DM/Q study, twenty patients with unipolar TRD were enrolled in an open-label study of DM/Q up to 45/10mg by mouth administered every 12h over the course of a 10-week period, and constituted the intention to treat (ITT) sample. For the ezogabine study, eighteen subjects with MDD were enrolled in an open-label POC study of ezogabine titrated to 900mg daily with resting state functional MRI (fMRI) collected at baseline and end of treatment (week 10). For the minocycline study, twenty patients with bipolar depression were enrolled in an 8-week, open-label trial of adjuvant minocycline and proton magnetic resonance spectroscopy (1H MRS) measures of cortical glutathione (GSH) were obtained before and after treatment.
Results: All three agents showed tolerability and a preliminary efficacy signal within the context of the open-label design. Following DM/Q, Montgomery-Asberg Depression Rating Scale (MADRS) score was reduced from baseline to the 10-week primary outcome (mean change: -13.0 ± 11.5, $p<0.001$). The response and remission rates were 45% and 35%, respectively. Following ezogabine, MADRS score significantly decreased at study end [−13.7 ± 9.6, $p<0.001$], with greater improvement in depression associated with reduced connectivity between the ventral striatum and the anterior mid-cingulate (whole-brain cluster corrected $p<0.05$,). Following minocycline, depression severity improved significantly [MADRS score change: -14.6 (95% CI: -7.8 to -21.3)] and higher baseline GSH levels were associated with greater improvement in MADRS score following treatment ($\rho=0.51$, $p=0.05$).
Conclusions: Data are presented for three mechanistically novel antidepressant candidates. Across the agents, these interventions showed good tolerability and preliminary efficacy. Mechanistic data gathered in these trials provides early information concerning potential mechanisms of action in humans.

Learning Objectives

1. To understand mechanistically novel approaches to treatment development for mood disorders, and for treatment-resistant depression in particular.
2. To learn about the potential of agents targeting molecular pathways to enhance cellular resilience as novel therapies for treatment-resistant depression and other forms of mood disorders.

Literature References

1. Friedman AK, Juarez B, Ku SM, Zhang H, Calizo RC, Walsh JJ, Chaudhury D, Zhang S, Hawkins A, Dietz DM, Murrough JW, Ribadeneira M, Wong EH, Neve RL, Han M-H: KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. Nat Commun 2016; 7:11671
2. Murrough JW, Abdallah CG, Mathew SJ: Targeting glutamate signalling in depression: progress and prospects. Nat Rev Drug Discov 2017; 16:472–486

ANTIDEPRESSANT EFFECTS OF DEEP PROPOFOL ANESTHESIA

Brian Mickey, University of Utah School of Medicine

Individual Abstract: Background: About one-third of individuals with depression do not respond to conventional first-line treatments, and novel interventions are sorely needed. Antidepressant effects have been demonstrated with agents that target glutamate and gamma-

aminobutyric acid (GABA) neurotransmitter systems. We hypothesized that propofol -- a unique, well-tolerated, general anesthetic with effects on glutamate and GABA neurotransmission -- would have antidepressant effects.
Methods: To collect preliminary evidence of efficacy and tolerability, we are conducting an open-label trial of deep propofol anesthesia. Thus far, seven outpatients with moderate-to-severe, treatment-resistant depression (age 20-45 and otherwise healthy) have been recruited from a specialty referral clinic. All were considered good candidates for electroconvulsive therapy. Propofol was administered during a series of 10 treatment sessions and dosed individually to induce strong suppression of electroencephalographic activity. The primary outcome measure was the 24-item Hamilton Depression Rating Scale (HDRS-24). Cognitive function was monitored using the Montreal Cognitive Assessment (MoCA).
Results: The HDRS-24 total score decreased by a mean of 28 points (range 9-45 points; $p=0.002$), corresponding to a mean 77% improvement (range 38-100%). Six of the 7 subjects met criteria for response (>50% improvement) and 5 of 7 met criteria for remission (HDRS-24<10). Side effects were mild and temporary. MoCA total score was unchanged. No participant reported cognitive side effects or left the trial early. No serious adverse events occurred.
Conclusions: The findings of this open-label trial suggest that high-dose propofol has antidepressant effects similar in magnitude to electroconvulsive therapy, and with fewer side effects. Deep propofol anesthesia was well tolerated in this physically healthy cohort. A blinded randomized controlled trial of propofol is warranted.

Learning Objectives

1. To understand that deep anesthesia with propofol had antidepressant effects in a small open-label trial.
2. To appreciate that propofol had antidepressant effects similar in magnitude to ECT but without cognitive side effects.

Literature References

1. Kingston S, Mao L, Yang L, Arora A, Fibuch EE, Wang JQ (2006). Propofol inhibits phosphorylation of N-methyl-D-aspartate receptor NR1 subunits in neurons. Anesthesiology 104(4): 763-769.
2. Orser BA, Bertlik M, Wang LY, MacDonald JF (1995). Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. Br J Pharmacol 116(2): 1761-1768.

ENHANCING MEDICATION ADHERENCE IN CLINICAL TRIALS: CHALLENGES AND OPPORTUNITIES

Mary Rooney, National Institute of Mental Health

Overall Abstract: Poor adherence in clinical trials leads to reduced statistical power, biased estimates, and limitations surrounding the conclusions that can be drawn from study findings (Brekenridge et al., 2017). Traditional methods of adherence monitoring (e.g., retrospective self-report data, pill counts), underestimate poor adherence and fail to measure the multiple constructs that underlie adherence (Blaschke et al., 2012). Adherence is increasingly understood as a multifaceted concept (e.g., medication regimen initiation, implementation, and

persistence). Each dimension of adherence may have unique determinants, and each may require distinct interventions (Pakpour et al., 2017).

The panel presenters draw upon randomized controlled trial data to address multiple dimensions of adherence. Our first presenter, Dr. Kane, will anchor his presentation with a discussion of the adherence findings from the NIMH-funded RAISE study, and the conclusions that can and cannot be drawn based on the adherence monitoring measures used in this trial (Robinson et al., 2017). Dr. Kane will also discuss recruitment outcomes and perspectives from trials of long-acting injectables (LAIs) in schizophrenia, highlighting LAIs as an existing medication delivery method that circumvents many of the adherence challenges inherent in daily oral medication regimens. Existing barriers to the routine use of LAIs in clinical practice will be discussed (Correll et al., 2016). Lastly, Dr. Kane will speak to recent technological advances that have the potential to improve patient adherence monitoring in schizophrenia clinical trials and in clinical practice.

Our second presenter, Dr. Sajatovic, will discuss differences and similarities between medication adherence challenges in schizophrenia and bipolar disorder (BD), and highlight the importance of multimodal adherence assessment. Dr. Sajatovic and her team have recently completed an NIMH-funded clinical trial (R01 MH93321) evaluating a brief, tailored intervention intended to improve medication adherence in high-risk patients with BD (Levin, Tatsuoka, Cassidy, Aebi, Sajatovic, 2015). Primary outcomes will be presented, and the implications of these findings will be discussed. Dr. Sajatovic will also present findings from an ongoing NIMH-funded data harmonization project (R01 MH093321-05S1) that has created a data repository for data from studies of aging in BD. The effects of adherence and medical burden in BD across the lifespan will be discussed. In addition, Dr. Sajatovic will highlight the importance of using common data elements in treatment research to promote large scale analyses in treatment research.

Our final presenter, Adam Hanina, MBA, co-founder and CEO of AiCure, will highlight the importance of remote patient monitoring to ensure drug exposure, optimize the likelihood of detecting a signal, and better understand how the investigational product works. Specifically, he will provide an overview of different patient monitoring approaches, a description of how the visual recognition platform operates as well as potential applications, present clinical evidence demonstrating drug concentration increases across different indications, highlight assistive and fraud-detection methodologies, and describe the future of active and passive monitoring and the introduction of objective endpoint assessments.

Our discussant, Dr. Rudorfer of NIMH, will comment on the implications of this work for informing adherence monitoring in future clinical trials, as well as the importance of moving toward the use common data elements to facilitate the harmonization of data across studies.

Learning Objectives

1. Understand how multiple determinants of medication adherence contribute to challenges in monitoring and adherence improvement.
2. Learn how breakthrough technologies and the use of common data elements in clinical trials can improve the value and impact of adherence monitoring data.

ADHERENCE IN SCHIZOPHRENIA: LESSONS LEARNED FROM RAISE-ETP, THE USE OF LONG ACTING INJECTABLES AND OTHER STRATEGIES

John Kane, The Zucker Hillside Hospital

Individual Abstract: Adherence in medication-taking remains an enormous challenge in any chronic illness, but particularly in an illness like schizophrenia. Even when coordinated specialty care is provided, as in the NIMH-funded RAISE-ETP project, hospitalization rates remain high and no difference in rates over two years of follow-up was found between coordinated specialty care (NAVIGATE) (34%) and usual community care (37%). However, a simple three question, self-administered instrument on attitudes towards medication-taking was a significant predictor of hospitalization in this population.

Although long-acting injectable (LAI) medications were not highly utilized in the RAISE-ETP project, data from an ongoing large simple trial involving LAI's in first episode and early phase patients indicates that a high proportion of eligible patients will entertain a trial of LAI's if it is presented to them in an appropriate fashion.

Despite evidence as to the potential benefit of LAI's they remain grossly underutilized particularly during the early phase of illness and strategies to increase utilization are an important area and will be discussed in this presentation.

In addition, we will review early experience with a "digital medicine" approach to the facilitation of adherence among patients with schizophrenia. This involves the use of a sensor ingested with the medicine to establish patterns in medication-taking and inform personalized treatment plans.

Given the impact of medication in preventing relapse and the personal and societal consequences of non-adherence, much remains to be done in this area.

Learning Objectives

1. To review the relationship between non-adherence and relapse/hospitalization in first episode schizophrenia.
2. To discuss obstacles to the use of long acting injectable antipsychotics particularly in early phase illness.

Literature References

1. Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, Addington A, Brunette MF, Correll CU, Estroff SE, Marcy P, Robinson J, Meyer-Kalos PS, Gottlieb JD, Glynn SM, Lynde DW, Pipes R, Kurian BT, Miller AL, Azrin ST, Goldstein AB, Severe JB, Lin H, Sint KJ, John M, Heinssen RK.Comprehensive Versus Usual Community Care For First Episode Psychosis: Two-Year Outcomes From The NIMH RAISE Early Treatment Program. American Journal of Psychiatry 2016; 173(4):362-372. PMCID: PMC4981493.
2. Robinson DR, Schooler NR, Correll CU, John M, Kurian BT, Marcy P, Miller AL, Pipes R, Trivedi MH, Kane JM. Psychopharmacological treatment in the RAISE-ETP study: Outcomes of a manual and computer decision support system based intervention. Am J Psychiatry. 2017 Sep 15:appiajp201716080919. doi: 10.1176/appi.ajp.2017.

TREATMENT ADHERENCE IN BIPOLAR DISORDER

Martha Sajatovic, University Hospitals Case Medical Center

Individual Abstract: Poor adherence in people with bipolar disorder (BD) is a pervasive problem that causes disability and suffering as well as extensive financial costs. Barriers to adherence are many and cross multiple levels including factors related to BD pathology and factors unique to an individual's genetic, psychological and social circumstances. The treatment setting, healthcare system and broader health policies all can impact medication

adherence in BD. Another factor impacting the variable non-adherence rates in the BD population can be attributed to the way medication non-adherence is defined and measured. Studies use objective, subjective, or both types of measurements to quantify medication adherence. While easy and practical, there may be a tendency for patients to over-report their level of adherence on self-report scales. Objective methods for measuring medication adherence include pill counts, serum drug levels, pharmacy refill records, and microchip placement on tablets. Though objective methods have the benefit of avoiding reliance on patient or caregiver report, they do present their own set of difficulties.

There are few evidence-based approaches that specifically target adherence in BD. A recently completed 6 month, prospective randomized, controlled trial (RCT) of a novel approach called customized adherence enhancement (CAE) vs. a BD-specific and rigorous educational intervention (EDU) in 184 poorly adherent individuals with BD found improved BD medication adherence (p=.03), functional status (p=.04) and less use of outpatient mental health services (p=.01) with CAE vs. EDU. CAE appears acceptable to individuals that are often not included in typical research studies (minorities, individuals with known poor adherence). In addition to adherence-focused studies, adherence evaluation needs to be an embedded component of observational and interventional BD trials. Ideally, adherence assessment can be considered in relation to other relevant health factors such as medical burden and cumulative medication "load". Large data-sharing repositories such as the National Institute of Mental Health Data Archive (NDA) includes human subject's data collected from numerous research projects across many scientific domains. The NDA provides infrastructure for sharing research data, tools and methods, and may be an additional avenue to study treatment adherence in BD and other psychiatric disorders. An ongoing challenge for the field will be to identify and standardize adherence assessment in clinical trials so that studies can be compared and aggregate data secondary analyses optimized.

Learning Objectives

1. Participants will gain familiarity with various methods of adherence evaluation in individuals with bipolar disorder.
2. Participants will learn about adherence-enhancement approaches specific to bipolar disorder.
3. Participants will better understand the potential for large shared data repositories to investigate cross-cutting issues in adherence research.

Literature References

1. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70 Suppl 4:1-46.
2. Levin, J. B., Krivenko, A., Howland, M., Schlachet, R., & Sajatovic, M. Medication Adherence in Patients with Bipolar Disorder: A Comprehensive Review. CNS Drugs, 2016;30(9), 819-835.

ENHANCING MEDICATION ADHERENCE IN CLINICAL TRIALS: CHALLENGES AND OPPORTUNITIES

Adam Hanina, AiCure

Individual Abstract: Objective: Remote patient monitoring is critical to ensuring optimal drug exposure, which in turn increases the likelihood of detecting a signal and improves our

understanding of how a drug works. Poor adherence to the medication and to protocol requirements reduces statistical power and impacts the quality of decision-making in drug development. Currently, clinical trials rely on a variety of direct and indirect measures to assess medication adherence; yet these measures present inherent difficulties, and none has been validated to improve protocol compliance and heighten drug exposure. An artificial intelligence (AI) platform that uses software algorithms on smartphones to visually and automatically confirm medication ingestion has been used to measure and maximize medication adherence in CNS studies. Aggregated data demonstrate the feasibility of using the platform in challenging patient populations, improve data quality and impact trial outcome.
Design: Aggregated data were collected from CNS studies across six indications. Study designs varied by treatment duration, inclusion/exclusion criteria, dosing regimens, packaging, dosing setting, and assessment frequency (six to 52 weeks' treatment duration, ages 16-65 years, dosing QD or BID, 1-5 units per dose, bottles or blister packs, inpatient and outpatient, weekly/bi-weekly/monthly clinic visits). Study subjects were provisioned with smartphones or used their own smartphone and asked to use the AI application for each dosing administration. In addition to tracking medication intake, the patient-facing interface also provided automated reminders, alarms, dosing windows, clinic visit scheduling, and protocol-specific dosing instructions. Study teams and sites had access to data, analytics, automated notifications, and intervention escalation protocols.
Results: 58,803 adherence parameters were collected in studies with total target enrollments of 1,277 subjects. For randomized subjects who received at least 1 dose of the study drug, cumulative average adherence as measured by the AI platform (visual confirmation of ingestion) across all treatment groups, including placebo, was 85.2%. On the basis of PK sampling, mean adherence was 90.2% (PK adherence was defined as drug levels greater than the lower limit of quantification (LLOQ)). Average retention rate was 78.4% and average rate of fraudulent activity (intentional misuse of the technology) ranged from 3.8% to 12.3%. Subjects received an average of 3.1 site interventions (50.1% text messages; 43.2% phone calls; 6.7% in-person clinic visits). Approximately 75% of subjects ceased fraudulent activity or were withdrawn from the study based on interventions. AiCure data were used in most studies as the primary measure of adherence for at-home and in-clinic dosing (at the time of PK sampling).
Conclusion: Subjects in CNS trials across multiple indications were able to use the technology correctly and consistently. Remote patient monitoring in CNS trials allowed for the collection of accurate dosing data, improved data quality, and increased compliance and drug exposure based on PK data. Validation of the technology was based in part on concordance between data registered on the AI platform and PK data. Use of the AI Platform allowed for post-hoc analyses in determining whether a drug was effective and whether a drug worked sub-optimally because subjects were non-adherent. Future remote patient monitoring using artificial intelligence will include active and passive monitoring and the introduction of exploratory endpoint assessments.

Learning Objectives

1. Participants will gain familiarity with various methods of adherence evaluation currently in use in CNS studies.
2. Participants will learn about remote patient monitoring and the impact of accurate data on trial outcome. Participants will better understand the potential of artificial intelligence in future remote patient monitoring, exploring new endpoint assessments based on active and passive data.

Literature References

1. McCann DJ, Petry NM, Bresell A, et al: Medication nonadherence, "professional subjects," and apparent placebo responders: overlapping challenges for medications development. J Clin Psychopharmacol 2015; 35:566-573.
2. Bain EE, Shafner L, Walling DP, Othman AA, Chuang-Stein C, Hinkle J, Hanina A. Use of a novel artificial intelligence platform on mobile devices to assess dosing compliance in a Phase 2 clinical trial in subjects with schizophrenia. JMIR Mhealth Uhealth. 2017; 5: e18.

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

RANDOMIZED, DOUBLE-BLIND STUDY OF FLEXIBLY-DOSED INTRANASAL ESKETAMINE PLUS ORAL ANTIDEPRESSANT VS. ACTIVE CONTROL IN TREATMENT-RESISTANT DEPRESSION

Vanina Popova[1], *Ella Daly[1], Madhukar Trivedi[2], Kimberly Cooper[1], Rosanne Lane[1], Pilar Lim[1], David Hough[1], Michael E. Thase[3], Richard Shelton[4], Patricio Molero[5], Eduard Vieta[6], Malek Bajbouj[7], Husseini Manji[1], Wayne C Drevets, MD[8], Jaskaran Singh[1]*

[1]Janssen Research & Development, LLC, [2]UT Southwestern Medical Center, [3]Perelman School of Medicine at the University of Pennsylvania, [4]University of Alabama at Birmingham, [5]Clinica Universidad de Navarra, [6]Hospital Clinic, University of Barcelona, [7]Charité Universitätsmedizin Berlin, [8]Laureate Institute for Brain Research, Janssen Research and Development

Abstract: Background: About 30% of the patients with major depressive disorder (MDD) fail to achieve remission despite treatment with multiple antidepressant medications, and are considered to have treatment-resistant depression (TRD).
Methods: This was a Phase 3, double-blind, active-controlled, multicenter study (NCT02418585) using blinded raters, conducted at 39 sites in Spain, Germany, Czech Republic, Poland, and the United States from August 2015 to June 2017. The study enrolled adults with moderate-to-severe, non-psychotic, recurrent or persistent depression, and history of non-response to ≥2 antidepressants in the current episode of depression, with 1 of them assessed prospectively. Non-responders were randomized (1:1) to flexibly-dosed intranasal esketamine (56 or 84 mg twice weekly) and a new oral antidepressant or intranasal placebo and a new oral antidepressant (active control). The primary efficacy endpoint – change from baseline to endpoint (day 28) in Montgomery-Asberg Depression Rating Scale (MADRS) total score – was assessed among patients who received ≥1 dose of (intranasal and oral) study medication by mixed-effects model using repeated measures. Remission rate, a secondary endpoint, was assessed using Generalized Cochran-Mantel-Haenszel (CMH) test, adjusting for country and class of oral antidepressant (SNRI or SSRI) as a post hoc analysis.
Results: 435 patients were screened, 227 randomized, and 197 completed the double-blind period. Change (LS mean [SE] difference vs. placebo) in MADRS total score with intranasal esketamine and oral antidepressant was superior to oral antidepressant and intranasal placebo at day 28 (-4.0 [1.69], 95% CI: -7.31, -0.64; one-sided p=0.010), as well as at earlier timepoints (one-sided p≤0.009 at 24 hours postdose and days 8 and 22). Remission rate (MADRS total score ≤12) at day 28 was 52.5% (53/101) and 31.0% (31/100) for the respective groups (one-

sided p=0.001). The most common adverse events reported for the esketamine plus oral antidepressant group were dysgeusia, nausea, vertigo, and dizziness; the incidence of each (20.9-26.1%) was >2-fold higher than for the oral antidepressant plus intranasal placebo group. Conclusions: Robust efficacy of intranasal esketamine and superiority to an active control were demonstrated on the primary efficacy endpoint result. More than half of the esketamine-treated TRD patients achieved remission by the 4-week endpoint. Favorable safety and tolerability of intranasal esketamine reported in this study suggest a positive risk-benefit profile of intranasal esketamine.

A PROOF-OF-MECHANISM STUDY OF THE PDE10 INHIBITOR RG7203 IN PATIENTS WITH SCHIZOPHRENIA AND NEGATIVE SYMPTOMS PROBING REWARD FUNCTIONS WITH IMAGING AND BEHAVIORAL APPROACHES

Daniel Umbricht[1], *Jürgen Dukart[1], Markus Abt[1], Paul Tamburri[1], Chris Chatham[1], Michael Frank[2], Anne Collins[2], David Walling[3], Rick Mofsen[4], Daniel Gruener[5], Lev Gertsik[6], Jeff Sevigny[1]*

[1]F. Hoffmann-La Roche Ltd, [2]Brown University, [3]CNS Network, LLC, [4]Evolution Research Group, [5]St Louis Clinical Trials, [6]CCT

Abstract: Background: The enzyme phosphodiesterase 10A (PDE10A) is highly expressed in the striatum where it modulates both dopamine D2 and D1 dependent signaling. Its inhibition leads to a suppression of D2 mediated signaling –similar to effects of D2 antagonists - and an enhancement of D1 dependent signaling. D1-dependent signaling has been implicated in reward based learning. Its deficient activation may be a key factor underlying deficient reward functions including reward anticipation and reward based learning that have been implicated as major drivers of negative symptoms of schizophrenia. Therefore inhibition of PDE10 could be a way to ameliorate such deficits and consequently negative symptoms. In healthy volunteers the PDE10 inhibitor RG7203 indeed enhanced performance in tasks that probed reward functioning suggestive of its potential utility to treat negative symptoms in schizophrenia. We therefore tested the hypothesis that it should enhance imaging and behavioral markers of reward functions in patients with moderate negative symptoms in order to establish mechanistic proof of its utility as treatment of negative symptoms.
Methods: In a three-way cross-over study we investigated the effects of two doses of RG7203 (5 mg and 15 mg) and placebo given as adjunctive treatment to stable background antipsychotic treatment on reward functioning and reward-based effortful behavior using the monetary incentive delay (MID) task during fMRI and the effort choice task in patients with chronic schizophrenia and moderate levels of negative symptoms (PANSS negative symptom factor score ≥ 18 points). Each treatment period lasted three weeks followed by a 2 week washout period. fMRI and behavioral tasks were administered at the end of each treatment period. Key outcome measures were the differential BOLD during reward anticipation and overall BOLD activity during the MID task and the percentage of high-effort high-reward choices when the probability of reward was 100% during the effort choice task.
Results: Thirty-three patients with schizophrenia (30 male; 21 B, 9 W, 3 A; mean age 36.6±7 y; PANSS NSFS = 22.8 (±1.4) at screening) were recruited at three study centers in the US. Twenty-four subjects finished the entire study. RG7203 at 5 mg significantly increased differential BOLD activity during reward anticipation in the MID task. However, this enhancement occurred in the context of a significant decrease of BOLD activity across all conditions during the MID task under treatment with RG7203 . RG7203 significantly worsened

reward-based effortful behavior in the effort choice task (the high-effort high-reward choice: 67% for both doses of RG7203 versus 73% for placebo). Multiple regression revealed that the decrease in effortful behavior was significantly related to the decrease in overall BOLD activity during the MID task and not related to the difference of BOLD activity during reward anticipation versus the control condition.
Conclusion: In contrast to our expectation and previous results in healthy volunteers, RG7203 worsened indices of reward functions which we hypothesize may be due to a further enhancement of D2 antagonistic activity. The results do not support the utility of a PDE10 inhibitor as adjunctive treatment for negative symptoms in patients with schizophrenia. Given the previous observation that RG7203 enhanced reward functions in healthy volunteers who were not treated with D2 antagonist, the results of our study point to potentially deleterious effects of D2 blockade on reward functions and by extension on negative symptoms of schizophrenia. They raise the question if the presence of D2 antagonistic treatment curtails the potential effects of any adjunctive treatment for negative symptoms.

MOVING BEYOND EFFICACY AND SAFETY TO REAL-WORLD USABILITY IN THE DIGITAL MEDICINE ERA

Timothy Peters-Strickland[1], *Cathy Zhao[1], Jonathan Knights[1], Tao Wang[1], Corey Fowler[1], Felicia Forma[1], Ross A. Baker[1]*

[1]*Otsuka Pharmaceutical Development and Commercialization, Inc.*

Abstract: Background: A Digital Medicine System (DMS) has been developed to objectively measure and report a patient's medication ingestion. The DMS consists of a medication-embedded ingestible sensor, wearable sensor (adhesive patch), and mobile- and cloud-based software applications that enable the secure collection and sharing of objective medication adherence information with healthcare professionals (HCP), family members and friends.
Objective: Test the usability of the DMS in adult subjects with serious mental illness (SMI) consisting of schizophrenia (SCH), bipolar 1 disorder (BP1) or adjunctive treatment of major depressive disorder (MDD) who are treated with oral aripiprazole.
Methods: A series of usability (NCT02219009; NCT02722967) and human factors engineering (HFE) studies were completed in order to support approval of the system by the US FDA. Patients with SCH, BP1, or MDD stabilized on oral aripiprazole were enrolled in two 8-week usability studies, and a series of human factor studies were conducted in patients with SMI, as well as (HCPs) and caregivers. The outcomes of the usability studies were the proportion of time during the trial period when the subject wears their patch, and ingestion adherence defined as the total number of ingested events registered on the digital health server/number of treatment days in the trial with good patch coverage.
Results: 122 patients were screened and 116 enrolled in the 2 usability studies; 87/116 (75.0%) completed the study. Mean ingestion adherence was 86%and mean proportion of patch wear was 74% for all 116 patients over the course of the 8-week studies; no differences were observed among patients with SCH, BP1, or MDD. In the HFE validation study, 35 subjects with SMI successfully completed 783 of 803 (97.5%) tasks involving the use of DMS. Residual risks resistant to mitigation were found to be of low severity based on the US FDA HFE guidance. An additional pragmatic clinical study will soon be initiated to measure longer-term clinical outcomes associated with DMS use vs. standard-of-care in a naturalistic, real-world setting.

Conclusions: The results of the usability and HFE studies conducted with the DMS were sufficient for FDA-approval of the first DMS; additional real-world data is important to understand the place of the DMS in clinical practice.
Disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc. All authors are full-time employees of Otsuka.

NIMH FAST-MAS PHASE IIA STUDY OF THE EFFECTS OF THE SELECTIVE κ OPIOID ANTAGONIST JNJ-67953964 ON FMRI VENTRAL STRIATAL ACTIVATION DURING THE MONETARY INCENTIVE DELAY TEST IN ANHEDONIC PATIENTS WITH MOOD AND ANXIETY SPECTRUM DISORDERS

Andrew Krystal[1], *Diego Pizzagalli[2], Moria Smoski[3], Sanjay Mathew[4], John Nurnberger[5], Sarah Lisanby[6], Dan Iosifescu[7], James Murrough[8], Richard Weiner[3], Joseph Calabrese[9], Gerard Sanacora[10], Richard Keefe[11], Steven Szabo[11], Wayne Goodman[4], William Potter[12]*

[1]UCSF, [2]Massachusetts General Hospital, [3]Duke University School of Medicine, [4]Baylor College of Medicine, [5]Indiana University, [6]NIH/NIMH, [7]Nathan S. Kline Institute/New York University School of Medicine, [8]Icahn School of Medicine at Mount Sinai, [9]University Hospitals Cleveland Medical Center, [10]Yale, [11]Duke University Medical Center, [12]National Institute of Mental Health

Abstract: Introduction: A compelling body of preclinical research suggests that κ opioid receptor (KOR) antagonism has promise as treatment for anhedonia, a core symptom of mood and anxiety spectrum disorders. However, we lack data on the effects of selective KOR antagonists in humans. We carried out this Phase IIa study under the New Experimental Medicine Studies: Fast-Fail Trials in Mood and Anxiety Spectrum Disorders (FAST-MAS) program to test the hypothesis that engaging this target with a highly selective KOR antagonist, JNJ-67953964 (formerly known as CERC-501 and LY2456302) modulates ventral striatal reward circuitry. This was intended to establish proof of concept (POC) that KOR antagonism has potential therapeutic effects on anhedonia and to serve as a model for the use of biomarker-based outcomes to establish POC in early phase drug development.
Methods: Subjects 21-65 years of age meeting DSM-5 criteria for either a mood disorder (Major Depressive Disorder or Bipolar I or II currently in a major depressive episode, N=70) or an anxiety disorder (Generalized Anxiety Disorder, Social Phobia, Panic Disorder or Post-Traumatic Stress Disorder, N=19) who had anhedonia (Snaith-Hamilton Pleasure Scale score ≥ 20), were randomized to 8 weeks of double-blind treatment with JNJ-67953964 10 mg (N=45) or placebo (N=44). A dose of 10 mg was selected based on prior positron emission tomography receptor occupancy data showing robust KOR antagonism. Primary outcome was assessed with fMRI in conjunction with a monetary incentive delay (MID) task that was administered at baseline and after 8 weeks of study drug administration. Analyses examined group activation differences during anticipation of monetary gain, contrasted with non-incentive trials. Mixed-model ANOVA queried average activation in an a priori bilateral accumbens area mask defined by the Harvard-Oxford Subcortical Atlas for each contrast of interest.
Results: A total of 67 subjects had data for the primary outcome measure both at baseline and during treatment and were included in the Intent to Treat sample. Mixed-model analyses revealed a significant Group x Time interaction in reward gain anticipation ($p < 0.01$) (a priori primary outcome), consistent with relatively greater change from baseline in ventral striatal activation during anticipation of gain with Study Drug vs placebo. JNJ-67953964 was not

associated with any serious adverse events and was generally well tolerated. Side-effects of more than mild severity occurring more than 5% more frequently with JNJ-67953964 than placebo were pruritis (11.1%), depression exacerbation (6.7%), and rash (6.7%).
Conclusions: The results of this study establish that KOR antagonism has the hypothesized effect on neural function, thereby establishing POC that engaging this target is a promising means of treating anhedonia. The findings also specifically suggest the promise of JNJ-67953964 as an anhedonia therapy. This study provides the basis for carrying out larger trials with KOR antagonists powered for the use of clinical endpoints to determine the clinical impact of engaging this target. It also serves as a model for novel, RdoC-based, early phase drug development methodology incorporating rigorous testing of whether engaging a target has a hypothesized effect on neural function as a means of establishing POC before proceeding to trials with downstream clinical endpoints.

EFFECTS OF THE KCNQ CHANNEL OPENER EZOGABINE ON FUNCTIONAL CONNECTIVITY OF THE VENTRAL STRIATUM AND CLINICAL SYMPTOMS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Aaron Tan[1], Sara Costi[1], Laurel Morris[1], Nicholas Van Dam[2], Marin Kautz[1], Alexis Whitton[3], Allyson Friedman[4], Katherine Collins[1], Gabriella Ahle[1], Diego Pizzagalli[3], Dan Iosifescu[5], Eric Nestler[1], Ming-Hu Han[1], James Murrough[1]

[1]Icahn School of Medicine at Mount Sinai, [2]University of Melbourne, [3]Harvard Medical School, [4]Hunter College, [5]New York University

Abstract: Major depressive disorder (MDD) is a leading cause of disability worldwide, yet current treatment strategies are limited in their mechanistic diversity, and are only partially effective. Recent evidence has highlighted a promising novel pharmaceutical target—the KCNQ-type potassium channel—for the treatment of depressive disorders, which may exert a therapeutic effect via functional changes within the brain reward system, including the ventral striatum. The current study assessed the effects of the KCNQ channel opener ezogabine (also known as retigabine) on reward circuitry and clinical symptoms in patients with MDD. Eighteen medication-free individuals with MDD currently in a major depressive episode were enrolled in an open-label study and received ezogabine up to 900 mg/day orally over the course of ten weeks. Resting state functional magnetic resonance imaging data were collected at baseline and post-treatment to examine brain reward circuitry. Reward learning was measured using a computerized probabilistic reward task. Ezogabine significantly reduced depressive symptoms (Montgomery-Asberg Depression Rating Scale score change: -13.7±9.7, $p<0.001$, $d=2.08$). It also significantly reduced anhedonic symptoms (Snaith-Hamilton Pleasure Scale score change: -6.1±5.3, $p<0.001$, $d=1.00$), even when controlling for overall depression severity. Improvement in depression was associated with decreased functional connectivity between the ventral caudate and clusters within the mid-cingulate cortex and posterior cingulate cortex (voxel-wise $p<0.005$, cluster-wise $\alpha<0.05$). In addition, a subgroup of patients tested with a probabilistic reward task (n=9) showed increased reward learning following treatment. These findings highlight the KCNQ-type potassium channel as a promising target for future drug discovery efforts in mood disorders.

MDMA-ASSISTED PSYCHOTHERAPY FOR TREATMENT OF CHRONIC POSTTRAUMATIC STRESS DISORDER (PTSD): FINDINGS FROM PHASE 2 CLINICAL RESEARCH TRIALS

Allison Feduccia[1], *Lisa Jerome[1], Michael Mithoefer[2], Berra Yazar-Klosinski[3], Amy Emerson[1], Rick Doblin[3]*

[1]MAPS Public Benefit Corporation, [2]Medical University of South Carolina, Charleston, [3]Multidisciplinary Assn. for Psychedelic Studies

Abstract: Background: The Multidisciplinary Association for Psychedelic Studies (MAPS) recently completed FDA-regulated Phase 2 clinical trials of MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). MDMA stimulates release of serotonin, and to a lesser extent (nor)epinephrine and dopamine, with a subsequent enhancement of oxytocin and cortisol. The combined neurobiological effects of MDMA increases compassion for self and others, reduces defenses and fear of emotional injury, while enhancing communication and capacity for introspection, all of which may facilitate the therapeutic process.
Methods: Six double-blind, placebo-controlled studies were carried out to investigate the use of administering MDMA during 2-3 psychotherapy sessions spaced a month apart that were each accompanied by 3 non-drug integrative therapy sessions. Participants with chronic PTSD and a Clinician Administered PTSD scale (CAPS-4) Total Score of 50 were enrolled in the studies.
Results: The primary endpoint occurred after 3 preparatory non-drug sessions, 2-3 MDMA-assisted psychotherapy sessions spaced a month apart, and non-drug integrative sessions. When data was pooled across the 6 studies, a significant group effect was detected in change in CAPS-4 Total scores (n=103, placebo subtracted Cohen's d effect size 0.9, $p<0.001$). At the primary endpoint, 23% (n=31) for placebo/comparator group (0-40 mg MDMA) and 53% (n=72) of active MDMA group (75-125 mg) no longer met PTSD criteria. Significant improvements in depression (Beck Depression Inventory-II, $p<0.05$) and sleep quality (Pittsburgh Sleep Quality Index, $p<0.05$) were also measured in the active MDMA groups. The cause of PTSD, whether from war, childhood abuse, or sexual assault, did not impact the treatment outcomes. Remarkably, at the 12-month follow-up visit 67.7% (n=90) participants did not meet criteria for PTSD, demonstrating the long-term durability of this novel treatment. Mirroring study measure findings, participants reported extreme gains in life outcomes, such as enhanced relationships and increased effectiveness at their jobs or the ability to return to work. Physiological vital signs and adverse event rates support an acceptable risk/benefit ratio.
Conclusion: MDMA treatment was well-tolerated, with good safety outcomes in these controlled clinical settings with limited administrations. FDA granted Breakthrough Therapy designation for MDMA-assisted psychotherapy for treatment of PTSD. Phase 3 trials at 15 sites in US, Canada, and Israel will commence in Spring 2018. If findings are replicated, MDMA-assisted psychotherapy could be a FDA-approved treatment for PTSD by 2021.

THE RELATIONSHIP BETWEEN COGNITION AND DEPRESSION IMPROVEMENT AMONG MDD PATIENTS BY NSI-189, A NEUROGENIC, PRO-COGNITIVE, ANTIDEPRESSANT COMPOUND

Gary Kay[1], Roger McIntyre[2], Katherine E. Burdick[3], Karl Johe[4], *Santosh Kumar[5], George Papakostas[6], Maurizio Fava[6]*

[1]Cognitive Research Corporation, [2]University of Toronto, University Health Network, [3]Brigham and Women's Hospital, Harvard Medical School, [4]Neuralstem, Inc., [5]JSS Medical Research, [6]Massachusetts General Hospital

Abstract: NSI-189 is a new chemical entity discovered based on its neurogenic activities on human hippocampal neural stem cells in vitro and in vivo mouse young normal hippocampus. Additionally, it has been found to stimulate synaptic remodeling of hippocampus in ischemic stroke model, reverse peripheral neuropathy in diabetic models, ameliorate cognitive impairment in radiation-induced brain injury model, and enhance LTP to supra-normal levels. The compound was recently tested for the treatment of major depressive disorder (MDD) in a Phase II double-blind trial as monotherapy in outpatients with MDD.
Using the sequential parallel comparison design (SPCD), 220 subjects were randomized to: NSI-189 40mg daily (n=44), NSI-189 80mg daily (n=44), or placebo (n=132) for 6 weeks (Stage 1). At the end of 6 weeks, placebo-treated subjects who were non-responders (defined as less than 50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS)) with a MADRS score greater than 15 were re-randomized to 6 weeks treatment with NSI-189 40 mg daily (n=22), NSI-189 80 mg daily (n=22), or placebo (n=22) (Stage 2). Patients on NSI-189 who completed Stage 1 continued the same dose for another 6 weeks.
The primary and secondary endpoints on various depression scales were previously presented, which were not significant on MADRS or HAM-D17 but significant on SDQ, QIDS-SR (Stage 2 only), and CPFQ. We also noted that the compound showed statistically significant advantages on certain objective cognitive measures of attention and memory in CogScreen battery. We have further analyzed the correlation between changes in core symptoms of depression versus changes in individual CogScreen variables. Select variables show statistically significant correlation between improved MADRS-6 or SDQ-44 scores and increased cognitive performance in NSI-189 treated group, while showing significant correlation between worsening depression and worsening cognitive performance in placebo non-responders. By analyzing such associations, we hope to derive composite CogScreen indices that can detect cognitive improvement by NSI-189 in MDD patients, both dependent and independent of their depression status.

EFFICACY AND SAFETY OF MIN-101: A NEW COMPOUND FOR THE TREATMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA A 12-WEEK RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL

Michael Davidson[1], *Jay Saoud[2], Corinne Staner[2], Remy Luthringer[3]*
[1]Tel-Aviv University, Sackler Faculty and Minerva Neurosciences, [2]PPRS, [3]Minerva

Abstract: Objective: To compare the efficacy, safety, and tolerability of MIN-101, a compound with high affinities for sigma 2 and 5-HT2A receptors, to placebo in treating negative symptoms, of patients with stable symptoms of schizophrenia.
Methods: This multi-national Phase 2b trial enrolled 244 patients diagnosed with schizophrenia who were symptomatically stable for ≥ 3 months prior to entering the trial and had scores ≥ 20 on the three factors negative subscale of the PANSS. Patients were randomized to daily monotherapy with MIN 101 32 mg, MIN-101 64 mg, or placebo in a 1:1:1 ratio. The primary endpoint was the PANSS negative symptom score based on the five factors (pentagonal) model. Secondary outcomes were the rest of the PANSS score, the CGI, the Brief Negative Symptoms Scale (BNSS), the Brief Assessment of Cognition in Schizophrenia (BACS), the

Calgary Depression Scale for Schizophrenia (CDSS), and the Personal and Social Performance (PSP) scale. Safety parameters included treatment-emergent adverse events (TEAE), clinical laboratory, vital signs, electrocardiograms, Sheehan-suicidality tracking scale (S-STS), and the Abnormal Involuntary Movement Scale (AIMS). The Mixed-Effect Model Repeated Measure (MMRM) was used for analyzing the efficacy data.
Results: Statistically significant and dose dependent reduction in the primary endpoint score was demonstrated for MIN-101 32 mg and 64 mg compared to placebo ($p \leq 0.022$; ES 0.45 .and ≤ 0.003; ES 0.58 respectively). The ES were particularly high ES=1.3 in the younger patients. The validity of effects on the primary endpoint was supported by similar effects on most of the secondary measurements including: PANSS three factors negative symptoms subscale, PANSS total score, CGI, CDSS, and PSP. There were no statistically significant differences in PANSS positive subscale scores between MIN 101 and placebo.
No weight gain or clinically significant changes in vital sings, prolactin levels, routine laboratory values, metabolic indices and extrapyramidal symptom scores (EPS) were observed. One patient on 64 mg MIN-101 was discontinued from the trial based on a-priori established QT interval prolongation criteria and a second one following an episode of syncope. Completion rates for randomized patients in this 12-week study were as follows: MIN-101 62 mg = 64%, MIN-101 32 mg = 58% and placebo = 53%. The three treatment groups were balanced on all demographic and illness-related baseline characteristics.
Conclusions: MIN-101 at dosages of 32 and 64 mg/day demonstrated statistically significant efficacy of medium ES in reducing negative symptoms and good tolerability in stable schizophrenia patients. Since positive symptoms and EPS did not change, the improvement in negative symptoms was not secondary to improvement in positive symptoms or EPS, suggesting that MIN-101 might be the first specific treatment to have a direct effect on negative symptoms.

LOFEXIDINE FOR TREATMENT OF OPIOID WITHDRAWAL SYMPTOMS: A DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL IN OPIOID-DEPENDENT SUBJECTS

Danesh Alam[1], *Mark Pirner[2], Thomas Clinch[2], Marc Fishman[3]*

[1]Northwestern Medicine Central Dupage, [2]US WorldMeds, LLC, [3]Johns Hopkins School of Medicine and Maryland Treatment Centers

Abstract: Introduction: The first and potentially most critical step in treating opioid use disorder is managing the severe opioid withdrawal symptoms (OWS) that inevitably emerge during discontinuation of the misused opioid. Patients commonly report OWS as the primary reason for continuing opioid use. Failure to effectively mitigate OWS may cause patients to abandon their attempt at recovery. Lofexidine is an alpha2-adrenergic receptor agonist that opposes the adrenergic hyperactivity resulting from opioid withdrawal. It is under development for treatment of OWS and facilitation of completion of opioid discontinuation. If FDA-approved, lofexidine would be the first non-opioid medication indicated for OWS treatment.
Methods: Men and women ≥18 years of age seeking treatment for dependence on short-acting opioids and meeting dependence criteria based on Mini International Neuropsychiatric Interview were randomized to placebo, lofexidine 0.6 mg qid (2.4 mg/day) or lofexidine 0.8 mg qid (3.2 mg/day) treatment for 7 days after abrupt opioid discontinuation. Short Opiate Withdrawal Scale of Gossop (SOWS-G), a validated, subject-rated, 10-item inventory of

common OWS was the primary outcome measure and study completion rate was the secondary outcome. Clinical Opiate Withdrawal Scale (COWS), a validated, clinician-rated, 11-item inventory of opioid withdrawal signs and symptoms, was a tertiary outcome. For SOWS-G and COWS, higher scores indicate worse OWS. Vital signs, ECGs, and adverse events (AEs) were monitored for safety.

Results: A total of 602 subjects (71% male; mean age 35 ±11 years) were randomized and received study drug. Most were dependent on heroin (83%). The differences from placebo in overall SOWS-G LS means were significant in both lofexidine groups (–0.21 for lofexidine 2.4 mg, P = .02; and –0.26 for lofexidine 3.2 mg, P = .003), indicating OWS improvement. A significantly greater proportion of lofexidine-treated subjects completed the 7-day trial: 41.5% in the 2.4-mg group (odds ratio [OR], 1.85; P = .007) and 39.6% in the 3.2-mg group (OR, 1.71; P = .02) vs 27.8% for placebo. Mean COWS scores were significantly lower in the lofexidine groups vs placebo on days 1-5 ($P \leq 0.01$). Most AEs were mild or moderate in severity. Hypotension, orthostatic hypotension, and bradycardia were the most frequent lofexidine-associated AEs but resulted in few study discontinuations (2% per AE).

Conclusions: Lofexidine significantly improved OWS and significantly increased completion of a 7-day opioid discontinuation treatment compared with placebo. AEs related to lofexidine's sympatholytic activity were most frequent but rarely severe enough to interfere with completion of the trial. Successful recovery from opioid dependence requires successful treatment of OWS, especially during the first several days of opioid withdrawal when symptom severity peaks. Lofexidine's anti-adrenergic mechanism of action provides a non-opioid treatment option that could be widely accessible to opioid-dependent patients through a variety of healthcare providers in both metropolitan and rural settings.

THE GABA-A RECEPTOR POSITIVE ALLOSTERIC MODULATORS BREXANOLONE IV AND SAGE-217 IN THE TREATMENT OF MOOD DISORDERS: RESULTS FROM RECENT PLACEBO-CONTROLLED STUDIES

Stephen Kanes[1], *Samantha Meltzer-Brody[2], Handan Gunduz-Bruce[1], Abdul Sankoh[1], Haihong Li[1], Ella Li[1], Helen Colquhoun[1], David Rubinow[3], Charles Zorumski[4], James Doherty[1], Jeffrey Jonas[1]*

[1]Sage Therapeutics, Inc., [2]UNC School of Medicine, [3]University of North Carolina, [4]Washington University of St. Louis

Abstract: Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and acts through synaptic and extrasynaptic GABA-A receptors to mediate phasic and tonic inhibition. Dysregulation of GABAergic signaling, including altered expression levels of GABA and GABA-A receptors or aberrations in functionally-linked stress pathways (i.e. the hypothalamic-pituitary-adrenal axis), is thought to be associated with mood disorders, such as postpartum depression (PPD) and major depressive disorder (MDD). Positive allosteric modulators (PAMs) of GABA-A receptors may offer a novel mechanism of action for exploration as potential PPD and MDD therapeutics.

Brexanolone iv (USAN; formerly SAGE-547 injection) is a soluble, proprietary formulation of the GABA-A receptor PAM allopregnanolone that is being developed as a potential therapy for PPD. To evaluate the efficacy and safety of brexanolone iv, three pivotal, double-blind, randomized, placebo (PBO)-controlled studies (Study A: NCT02614547; B: NCT02942004; C: NCT02942017) were conducted in women stratified by PPD severity (17-item Hamilton

Rating Scale for Depression [HAM-D] total scores of ≥26 in Studies A and B and 20-25 for in Study C). Treatment consisted of a 60-hour continuous inpatient infusion, and across the three studies, 107 women received PBO and 102 received brexanolone iv at a dose of 90 µg/kg/h (BRX90). Using pooled data, at Hour 60 (primary endpoint), there was a significantly larger mean reduction from baseline in HAM-D total score with BRX90 (-17.0) than with PBO (-12.8; p<0.0001). Significant treatment differences were also observed at Hour 24 (p=0.0012), Hour 48 (p<0.0001), Hour 72 (p<0.0001), Day 7 (p=0.0007), and Day 30 (p=0.0213). Brexanolone iv was generally well tolerated.

SAGE-217 is a novel GABA-A receptor PAM that was rationally designed for oral bioavailability and once daily dosing. A Phase 2, double-blind, randomized, PBO-controlled study evaluated the efficacy and safety of SAGE-217 in men and women with moderate to severe MDD (HAM-D total score ≥22). Patients received an evening dose of study drug for 14 days. At Day 15 (primary endpoint), the SAGE-217 group showed a significantly greater LS mean reduction from baseline in HAM-D total score versus the placebo group (-17.4 versus -10.3; p<0.0001). These significant differences from placebo were observed as early as Day 2 (p=0.0223) and were maintained through Day 28 (p=0.0243). SAGE-217 was generally well tolerated.

Brexanolone iv and SAGE-217 are examples of developmental programs for novel GABA-A receptor PAMs that showed rapid and sustained reductions in depressive symptoms. These results will support a regulatory filing this year for brexanolone iv for the treatment of PPD and continued development of SAGE-217 as a potential therapy for MDD.

A RANDOMIZED WITHDRAWAL, DOUBLE-BLIND, MULTICENTER STUDY OF ESKETAMINE NASAL SPRAY PLUS AN ORAL ANTIDEPRESSANT FOR RELAPSE PREVENTION IN TREATMENT-RESISTANT DEPRESSION

Ella Daly[1], *Jaskaran Singh[2], Madhukar Trivedi[3], Adam Janik[2], Honglan Li[2], Yun Zhang[2], Xiang LI[2], Rosanne Lane[2], Pilar Lim[2], Anna Duca[2], David Hough[2], Michael E. Thase[4], John Zajecka[5], Andrew Winokur[6], Ilona Divacka[7], Andrea Fagiolini[8], Wieslaw Cubala[9], Istvan Bitter[10], Pierre Blier[11], Richard Shelton[12], Patricio Molero[13], Husseini Manji[5], Wayne C. Drevets[14]*

[1]Johnson & Johnson PRD, [2]Janssen Research & Development, LLC, [3]UT Southwestern Medical Center, [4]Perelman School of Medicine at the University of Pennsylvania, [5]Rush University Medical Center, [6]UConn Health, [7]Vodopad.cz, Czech Republic, [8]Universita di Siena, [9]Medical University of Gdansk, [10]Semmelweis University, [11]University of Ottawa Institute of Mental Health Research, [12]University of Alabama at Birmingham, [13]Clinica Universidad de Navarra, Pamplona, [14]Laureate Institute for Brain Research; Janssen Research & Development

Abstract: Abstract will be provided on Tuesday, May 29, 2018 at 4:00 PM EDT.

Individual Research Report Session: Interventions for Bipolar and Psychotic Disorders* 4:15 p.m. - 5:15 p.m.

CARIPRAZINE TREATMENT OF BIPOLAR I DEPRESSION: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY

Willie Earley[1], *Maria Burgess[1], Ludmyla Rekeda[1], Regan Dickinson[1], Balázs Szatmári[2], György Németh[2], Roger S. McIntyre[3], Gary Sachs[4], Lakshmi N. Yatham[5]*

[1]Allergan, [2]Gedeon Richter Plc, [3]University Health Network, University of Toronto, [4]Bracket Global LLC, [5]University of British Columbia

Abstract: Patients with bipolar I disorder (BP-1) experience depressive symptoms three times more often than manic/hypomanic symptoms. Standard antidepressants, although frequently prescribed for the treatment of BP-1 depression, have demonstrated limited efficacy in clinical trials. Cariprazine (CAR), a dopamine D3/D2 receptor and serotonin 5-HT1A partial agonist, is approved for the treatment of adults with schizophrenia, manic or mixed episodes associated with BP-1, and is currently in development for treatment of BP-1 depression (monotherapy) and major depressive disorder (adjunctive). In this phase 3, randomized, double-blind, placebo (PBO)-controlled trial (NCT02670551), the efficacy, safety, and tolerability of CAR 1.5 mg/d and 3 mg/d compared with PBO was evaluated in adults with BP-1 depression.

This was a 6-week, randomized, double-blind, PBO-controlled, parallel-group trial of 2 CAR doses in adults (18-65 years) who met DSM-5 criteria for BP-1 with a current depressive episode of ≥4 weeks and <12 months. Those with current psychotic features were excluded. Patients also had 17-item Hamilton Depression Scale (HAMD-17) total score ≥20 and ≥2 on item 1 (depressed mood), Clinical Global Impression – Severity (CGI-S) score ≥4, and Young Manic Rating Scale (YMRS) score ≤12. Participants were randomized 1:1:1 to CAR 1.5 mg/d (n=160), 3.0 mg/d (n=165), or PBO (n=163). Primary and key secondary efficacy parameters were change from baseline to week 6 on Montgomery-Åsberg Depression Rating Scale (MADRS) total score and CGI-S score, respectively. Least squares mean difference (LSMD) were estimated using a mixed model for repeated measures. Additional endpoints included MADRS response (≥50% reduction from baseline) and remission (total score ≤10) rates compared to PBO. AEs, routine laboratory tests, vital signs, and suicide risk were monitored.

CAR 1.5 mg/d and 3.0 mg/d were significantly more effective than placebo in improving depressive symptoms on the primary efficacy parameter. At week 6, CAR 1.5 mg/d and 3.0 mg/d showed a statistically significantly greater improvement in the adjusted mean change from baseline in MADRS total score over PBO by -2.5 (P=.0331) and -3.0 (P=0.0103), respectively. Both CAR doses decreased CGI-S scores compared to PBO: 1.5 mg/d, LSMD: -0.2 (P=0.0714) and 3.0 mg/d LSMD: -0.3 (P=0.0662), but these changes did not reach statistical significance. MADRS response rates at week 6 compared to PBO (39.7%) were significantly greater with CAR 3.0 mg/d (51.8%; P=0.0243), but not significant for CAR 1.5 mg/d (48.1%; P=0.1300). Importantly, both CAR 1.5 mg/d and 3.0 mg/d significantly increased remission rates on MADRS at week 6 (33.1%, P=0.0374; and 32.3%, P=0.0391, respectively) compared to PBO (23.1%).

The most frequently observed treatment-emergent AEs, ≥5% in either CAR group and twice the rate of PBO, were nausea, akathisia, dizziness, somnolence, and sedation. Mean change at week 6 for metabolic parameters were generally comparable between both CAR groups and PBO, mean weight change at week 6 was +0.5 kg for both cariprazine groups, compared to -0.27 kg for PBO.

Cariprazine at 1.5 and 3.0 mg/d is safe and effective in reducing depressive symptoms in adults with BP-1 disorder.

**Of Special Interest to Clinicians*

Learning Objectives

1. Review unmet need for treatment in bipolar I disorder depression and educate on promising new treatment option.

Literature References

1. Kupka RW AL, Nolen WA, Suppes T, et al: Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord 2007; 9:531-535.
2. Durgam S, Earley W, Lipschitz A, et al: An 8-Week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry 2016; 173(3):271-281.

COMPARISON OF THE EFFICACY AND SAFETY OF ATYPICAL ANTIPSYCHOTICS FOR THE TREATMENT OF SCHIZOPHRENIA BETWEEN ADOLESCENTS AND ADULTS

Shamir Kalaria[1], *Mathangi Gopalakrishnan[2], Islam Younis[3], Ramana Uppoor[3], Mehul Mehta[3], Tiffany Farchione[3], Mitchell Mathis[3], Hao Zhu[3]*

[1]University of Maryland School of Pharmacy, [2]University of Maryland, Baltimore, [3]FDA

Abstract: Objective: Although the typical onset of schizophrenia occurs in young adulthood (18-25 years old), adolescent onset is not uncommon, with an incidence upwards of 1%. Despite several reported differences in initial presentation, the overall goal of treatment in adolescent patients with schizophrenia remains identical to that of adult schizophrenia: to ameliorate the severity of positive and negative symptoms and improve the overall function of the patient. Currently, only six antipsychotics have been approved in the adolescents, thus attributing to widespread off-label use of other atypical antipsychotics. Considering that the use of antipsychotic treatment is the standard of care across the course of schizophrenia, special attention must be made to efficacy and safety in the adolescent population. The objective of this study is to qualitatively compare the efficacy and safety of atypical antipsychotics for the treatment of schizophrenia in adults and adolescents.

Methods: An adult and pediatric schizophrenia database was constructed using sponsor submitted applications to the U.S. Food and Drug Administration (FDA) and consisted of nine adult (N=17,778) and six adolescent (N=2,122) second generation antipsychotic programs. Similarity of antipsychotic-specific dose-response relationships were assessed using change from baseline in total positive and negative syndrome scale (PANSS) scores. Differences in major adverse effects were analyzed using FDA authored reviews and approved products labels.

Results: Placebo response was found to be similar between adults and adolescents across all acute schizophrenia trials. Similar trends in dose response relationships were also observed between both populations. Adolescent programs that failed to demonstrate efficacy were also determined to have similar trends in placebo and dose response as compared with adults. With regards to trial design, adult patients experienced a higher dropout rate (45%) as compared to adolescents (27%). Although no new adverse events were found in adolescent trials, differences in sedation, metabolic changes, and extrapyramidal symptoms were present between adults and adolescents.

Conclusions: The qualitative analysis demonstrates similarity in efficacy between adults and adolescents. However, existing differences in safety profiles warrant further monitoring in the

adolescent population. The results of this study provide a potential path for the extrapolation of efficacy in adolescents for the treatment of schizophrenia.

Learning Objectives

1. Evaluate similarity of dose-response relationships of currently approved antipsychotics between adults and adolescents.
2. Identify key differences in safety profiles between adults and adolescents and their potential implications to drug development.

Literature References

1. Agency for Healthcare Research and Quality: First and second generation antipsychotics in children and young adults: systematic review update. Comparative Effectiveness Review. 2017; 184: 26-66.
2. National Institute for Health and Care Excellence: Psychosis and schizophrenia in children and young people: Evidence Update. NICE guideline, 2015.

PIMAVANSERIN: POTENTIAL TREATMENT FOR PSYCHOTIC SYMPTOMS ACROSS NEURODEGENERATIVE DISEASES

Clive Ballard[1], Jeffrey Cummings[2], Pierre Tariot[3], James Owen*[1], Jim Youakim[1], Erin Foff[1], James Norton[1], Srdjan Stankovic[1]*

[1]ACADIA Pharmaceuticals, Inc., [2]Cleveland Clinic Lou Ruvo Center for Brain Health, [3]Banner Alzheimer's Institute and University of Arizona College of Medicine

Abstract: Psychosis is a common occurrence in the disease progression of patients with dementia. The reported prevalence of psychotic symptoms in patients across dementia types ranges from approximately 20 to 90%. Atypical antipsychotics are frequently used to treat these disorders, despite overall modest and inconsistent efficacy and significant safety concerns. In spite of the significant medical need, there is currently no pharmacologic treatment approved for dementia-related psychosis.

Pimavanserin (PIM), a selective 5-HT2A inverse agonist/antagonist was approved in the U.S. for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). This approval was based on a clinical trial program in patients with PDP. In addition to improving hallucinations and delusions in PDP patients, PIM showed benefit on clinical global impression of illness, nighttime sleep, daytime wakefulness, and reduced caregiver burden. Additionally, there was improvement seen in patients both without cognitive impairment and the subgroup of patients with mild cognitive impairment. Overall, patients in the PIM group experienced a statistically significant improvement in SAPS-PD scores from baseline to Day 43 compared with placebo (PBO) (5.79 vs. 2.73; p=0.001). In the subgroup analysis stratifying by baseline Mini-Mental State Examination (MMSE) score, the change from baseline to Day 43 for PIM compared with PBO in the cognitively-impaired group (N=50) was larger (7.11 vs. 0.47; p=0.002).

An additional Phase 2 study with PIM in Alzheimer's disease psychosis was recently completed. In this study, the mean MMSE score at baseline was 10.3 for the PIM group versus 9.8 for the PBO group. The study met its primary efficacy endpoint of improvement in psychotic symptoms at Week 6 of treatment as measured with the Neuropsychiatric Inventory-Nursing Home Version psychosis scale (hallucinations+delusions domains) (NPI-NH PS). On the primary endpoint, PIM had a 3.76-point improvement in psychosis at Week 6 compared to

a 1.93-point improvement for PBO (delta = -1.84, Cohen's d = -0.32, p=0.0451). Moreover, in the prespecified subgroup of participants with baseline NPI NH PS ≥12 a substantively larger treatment effect was observed compared with participants with NPI NH PS <12 (delta = -4.43, Cohen's d = -0.734, p=0.0114). Response, defined as ≥30% improvement, was observed in 55.2% versus 37.4%, p=0.0159, and for a ≥50% improvement 50.6% vsversus34.1%, p=0.0240, for PIM and PBO, respectively. In a post-hoc analysis of patients with NPI-NH PS ≥12, this was even more robust with ≥30% improvement observed in 88.9% vs. 43.3%, p=0.0004, and for a ≥50% improvement 77.8% vs. 43.3%, p=0.0084, for PIM and PBO, respectively. With respect to safety, PIM appeared to be well-tolerated in this elderly and frail patient population and did not have negative impact on cognition over either 6 or 12 weeks of treatment as assessed by MMSE.

The results of this study, coupled with the earlier tolerability and safety observations in cognitively impaired Parkinson's disease patients provided scientific foundation for the ongoing study of PIM for treatment of subjects with dementia-related psychosis associated with the most common neurodegenerative disorders. The study employees a relapse-prevention design and the endpoint of time to relapse of psychosis to evaluate the efficacy and safety of PIM for dementia-related psychosis in a long-term (chronic) treatment paradigm. The scientific rationale and justification for this approach will be discussed.

Learning Objectives

1. Review the clinical development program for pimavanserin.
2. Discuss the similarities of psychosis across dementia subtypes and the development of a trial to assess pimavanserin for dementia related psychosis.

Literature References

1. Ballard C, Banister C, Khan Z, Cummings J, Demos G, Coate B, Youakim J, Owen R, Stankovic S. Evaluation of the efficacy, tolerability, and safety of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: phase 2, randomised, placebo-controlled, double blind study. Lancet Neurol. 2018;(in Press).
2. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, Ballard C. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383:533-540.

Individual Research Report Session: Biomarkers and Neural Correlates
4:15 p.m. - 5:30 p.m.

EPIGENETIC MECHANISMS IN SUBSTANCE USE DISORDER QUANTIFIED BY NON-INVASIVE PET IMAGING

Changning Wang[1]

[1]*Harvard Medical School/Massachusetts General Hospital*

Abstract: Effective treatment and prevention of substance use disorder (SUD) remains a major health issue due to our limited understanding of the underlying pathophysiology and neurocircuitry changes necessary for successful therapy. In the past decade, research on epigenetics has revealed that SUD may have a strong connection with dysfunction of

chromatin-modifying enzymes, and among them, histone deacetylases (HDACs) are frequently implicated in SUD such as Alcohol Use Disorder (AUD). The rodent studies have demonstrated that the treatment with ethanol in rodents could upregulate the histone acetylation levels in several brain regions, such as prefrontal cortex. In addition, several HDAC isoforms, such as HDAC2 and HDAC3, are reported to increase as the treatment of ethanol in human neuronal cell line or in amygdala. The pan-HDAC inhibitors, trichostatin A (TSA) and sodium butyrate, as well as class I selective HDAC inhibitor (MS-275), have been tested in animal models. The treatment of these HDAC inhibitors could reverse ethanol-induced tolerance, anxiety, and ethanol drinking with upregulated histone acetylation level in the amygdala of rats. The treatment could reduce ethanol-induced behaviors and diminished the motivation to consume ethanol as well.

HDACs, therefore, hold a great potential as therapeutic targets and the investigation on HDAC expression changes in the development of AUD will directly advance understanding of the importance of epigenetic role in the neurobiology of AUD. As a critical next step, a key goal of this proposal is to measure HDAC density and distribution in AUD patients in vivo as a function of sex. Until recent developments from our lab, the density and distribution of HDAC in the brain could not be quantified without sampling tissue.

The first radiotracer, [11C]Martinostat, for non-invasive HDAC imaging in humans via positron emission tomography (PET) from our lab was recently approved by the FDA for first-in-man studies (IND # 123154). Our lab has now successfully imaged healthy adults (18-65 years old) using [11C]Maritnostat. The imaging data are quite promising and are already providing insights into regional HDAC expression. These data represent a major step forward in understanding epigenetic mechanisms in vivo.

We hypothesize that changes in HDAC enzyme expression in AUD can be mapped visually and quantitatively within the living brain by PET. In this abstract, we will report our progress on measuring HDAC density and distribution in the human brain using a unique brain-specific simultaneous magnetic resonance (MR) and PET scanner with [11C]Martinostat, which will deliver answers to fundamental questions about chromatin modifying enzymes in the human brain in a way that has not been possible until now.

Learning Objectives

1. Application of biomedical imaging in human diseases.
2. Investigation of epigenetics in substance use disorders.

Literature References

1. Wang C, Schroeder FA, Wey HY, et a: In vivo imaging of histone deacetylases (HDACs) in the central nervous system and major peripheral organs. J Med Chem 2014; 57:7999-8009.
2. Wey H-Y, Gilbert TM, et al: Insights into neuroepigenetics through human histone deacetylase PET imaging. Science Translational Medicine. 2016; 351, 351ra106.

EPIGENETIC DISINHIBITION OF FKBP5 BY AGING AND STRESS CONTRIBUTES TO INFLAMMATION AND CARDIOVASCULAR RISK

Anthony Zannas[1]

[1]*Max-Planck Institute of Psychiatry*

Abstract: Aging and stress-related phenotypes are associated with increased inflammation and cardiovascular risk, but the underlying molecular mechanisms remain unclear. Here we

uncover a mechanism through which the stress-responsive immunophilin FKBP5 contributes to these relations. In four independent human cohorts (total n=2,818), FKBP5 DNA methylation consistently decreased with age at selected promoter CpGs, and this age-related demethylation was accelerated by childhood trauma and major depression and was associated with FKBP5 upregulation. Genome-wide analyses in peripheral blood linked FKBP5 upregulation with a proinflammatory profile and altered NF-κB-related gene networks. Mechanistically, FKBP5 overexpression in immune cells promoted chemokine secretion and NF-κB activity by strengthening the interactions of regulatory kinases of the NF-κB pathway. These effects on NF-κB were prevented by both genetic (CRISPR/Cas9-mediated) deletion and selective pharmacological inhibition of FKBP5. Notably, the age- and stress-regulated FKBP5 CpGs flank and moderated a functional NF-κB response element through which NFκB activation induces FKBP5 transcription. This positive feedback suggested that the age- and stress-related FKBP5 demethylation may initiate a vicious cycle of FKBP5-NF-κB interactions, contributing to inflammatory disease states; accordingly, this demethylation signature was present in individuals with a history of acute myocardial infarction. Together our findings identify FKBP5-NF-κB signaling as a mediator of stress-augmented peripheral inflammation with aging and potential contributor to cardiovascular risk, thus pointing to novel biomarker and treatment possibilities.

Learning Objectives

1. Understand the potential of lasting epigenetic signatures to serve as novel biomarkers for stress-related disorders.
2. Using FKBP5 as an example molecule, demonstrate an interdisciplinary approach that can identify novel treatment candidates for stress-related disorders.

Literature References

1. Zannas AS, Wiechmann T, Gassen NC, Binder EB. Gene-Stress-Epigenetic Regulation of FKBP5: Clinical and Translational Implications. Neuropsychopharmacology. 2016;41:261-274.
2. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, Ressler KJ. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008;299:1291-1305.

NEURAL CORRELATES OF EATING BEHAVIOR

Lawrence Maayan[1], *Allison Larr[1], Phil Reiss[2], Matthew Hoptman[1], Jay Nierenberg[1], Bennett Leventhal[3]*

[1]Nathan Kline Institute, [2]University of Haifa, [3]UCSF

Abstract: Introduction: Changes in ingestive behavior are a risk factor for cardiac, endocrine and oncologic disease and are symptoms of mood, eating and thought disorders. Prior research has described neural correlates of obesity, but the focus has rarely been on aspects in common with psychiatric illness,. most sample sizes have been small and none have included eating behavior.

Methods: 102 adults were recruited from the community, screened for psychiatric illness. After an overnight fast and a standardized 15 minute breakfast where consumption was recorded for macro and micronutrients, they had measures of body mass index (BMI) recorded and

underwent structural and functional neuroimaging including 10 minutes of recorded activity while at rest, resting state fMRI (rs-fMRI).
Blood oxygen label dependent (BOLD) signal across the brain was examined in correlation with 3.5 cc seed regions of interest in nucleus accumbens, insula, orbito-frontal cortex and inferior frontal gyrus selected from the literature for their relevance to psychiatric function. Results were analyzed using modified scripts of AFNI and FSL commands. Age was regressed out and connectivity was correlated with BMI and with proportion of calories from fat consumed during the test meal.
Results: BMI correlated with decreased connectivity between clusters in pre/postcentral gyrus and seeds in left (cluster size 259 voxels p=.0039) and right nucleus accumbens (318 voxels, p=.0058) but increased connectivity between an insula seed and medial temporal gyrus (566 voxels, p=00021). The proportion of calories from fat consumed correlated with decreased connectivity between a region including inferior frontal gyrus and insula and seeds in left (614 voxels, p=.00027) and right nucleus accumbens (901 voxels, p=.000024).
Conclusions: Obese participants showed connectivity consistent with increased salience of reward paired with decreased reward sensitivity. This supports the reward deficit model of behavioral addiction whereby increased consumption is associated with decreased reward. Those who consumed more fat had decreased fronto-striatal connectivity between inhibitory and reward regions. Insula and nucleus accumbens featured prominently, supporting their roles in both short- and long-term eating behavior and suggesting a mechanism underlying the relationship between psychiatric illness and disordered eating. Future work should include identification of directionality between obesity, inflammation and neural change to better identify preventative strategies in eating disorders, behavioral addiction and associated illness.

Learning Objectives

1. Understand neural correlates of obesity and eating behavior.
2. Become acquainted with role of insula and orbitofrontal gyrus in eating behavior.

Literature References

1. Maayan, L., Hoogendoorn, C., Sweat, V. & Convit, A., 2011. Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. Obesity (Silver Spring, Md.), pp. 19(7), 1382–1387.
2. Hoptman, M. J. et al., 2010. Amygdalofrontal Functional Disconnectivity and Aggression.

ASSOCIATION OF DEPRESSIVE AND SUICIDAL SYMPTOM IMPROVEMENT AFTER KETAMINE ADMINISTRATION WITH DEFAULT MODE CONNECTIVITY CHANGES

Jennifer Evans[1], *Elizabeth Ballard[1], Cristan Farmer[1], Allison Nugent[2], Carlos Zarate, Jr.[1]*

[1]National Institute of Mental Health, [2]NIMH, NIH, DHHS

Abstract: Background: Major Depressive Disorder (MDD) is associated with a heavy burden of disability and can also lead to suicidal thoughts, attempts and deaths. The heterogeneity of symptoms associated with MDD has been an obstacle to identifying specific neural correlates of the presence of depression as well as response to treatment. Ketamine, a glutamate modulator, is associated with rapid reductions in depressive symptoms, and is therefore an ideal model to assess rapid changes across depressive symptoms. The aim of the analysis was to investigate the association of depression symptom improvement with default mode network

(DMN) connectivity ketamine in patients with treatment-resistant depression (TRD) with a particular focus on changes in suicidality. A suicidality index was obtained from a previous exploratory factor analysis of several clinical and self-reported depression rating scales (MADRS, HAMD, BDI, SHAPS) and was used as measures of unidimensional constructs of depression. The suicidal thoughts subscale was evaluated in contrast with the MADRS scale in resting state scans across a double blind randomized placebo controlled cross-over clinical trial of ketamine in unmedicated MDD-TRD patients.

Methods: For this study, a cohort of 22 MDD subjects (ages 20-65, 14 female) received resting state fMRI scans (8 minutes with eyes closed on 3T GE HDx scanner, 3.75mm resolution) over the course of a double blind randomized placebo controlled cross-over ketamine infusion study. Scans that were acquired 2 days after infusion, either placebo or ketamine, are included in this analysis. Subject level data were preprocessed in AFNI (https://afni.nimh.nih.gov/) and included motion realignment, physiological correction for both heart and respiratory rate, and normalization to MNI space. The DMN was defined using a seed-based correlation method where the average time course from a 6mm radius sphere placed at the posterior cingulate cortex was correlated with all other brain voxels. The correlation values were converted to Z-scores using Fisher transform. Group analyses were performed with 3dLME using a linear mixed effects model with a fixed effect of scan type (ketamine or placebo), a random effect of subject and covariates for MADRS and suicidal thoughts. Group maps were family-wise error corrected to $p<0.05$.

Results: We find that there are distinct maps corresponding to the suicidal thoughts and the MADRS scales that are associated with DMN connectivity changes after ketamine administration. The main effects of suicidal thoughts and MADRS both show connectivity increases between the dorsolateral prefrontal cortex and PCC. There is a negative association of MADRS with connectivity change after ketamine administration in the insula, anterior and posterior cingulate, thalamus and caudate. Conversely, connectivity changes specific to suicidal thoughts were positive and found in the posterior cingulate and insula.

Discussion: The regions of connectivity change found in this study reflect those that are found in the literature. Changes in DLPFC support the improvement of the regulation of negative affect with symptom improvement after ketamine administration. Similarly, the insular and DMN connectivity changes fit with the triple-network model of dysfunction proposed in MDD. The apparent reversal in correlation of connectivity change between the scales requires further investigation to explore if this suggests distinct networks responsible for depressive and suicidal symptoms. In conclusion, these results may help provide and understanding of the potential neural underpinnings of symptom profiles both before and after rapid-acting treatment with ketamine.

Learning Objectives

1. To learn about resting state functional connectivity alterations in depression and after response to ketamine administration.
2. To discuss how changes in default mode network resting state functional connectivity are associated with behavioural measures of depression and suicidality.

Literature References

1. Ballard ED, Yarrington J, Farmer CA, et al: Parsing out the heterogeneity of depression: factor analysis across commonly used depression rating scales. Journal of Affective Disorders (in press).

2. Nugent A, Ballard E, Gould TD, et al: Ketamine has distinct electrophysiological and behavioural effects in depressed and healthy subjects. Mol Psychiatry. (in press).

Individual Research Report Session: Individualizing Treatment and Assessment*
4:15 p.m. - 5:30 p.m.

A COMPUTATIONAL APPROACH TO PSYCHOSIS DETECTION AND PERSONALIZED TREATMENT

Albert Powers[1], *Christoph Mathys[2], Philip Corlett[3]*

[1]CT Mental Health Center, Yale University, [2]SISSA, [3]Yale University

Abstract: Perception is an active process, characterized by the building of an internal model of our environment, blending incoming sensory evidence with prior beliefs about our environment. Within this framework, hallucinations may be thought to arise from an increased influence of these prior beliefs during perception.

To test this idea, we adapted a classic sensory conditioning paradigm to the functional imaging setting: participants were exposed to repeated pairings of a visual stimulus with an auditory stimulus and subsequently reported the perception of the auditory stimulus even when it was not present, contingent on the presence of the visual—conditioned hallucinations. We recruited four groups of participants: those with psychosis, both with hallucinations (P+H+) and without (P+H-), healthy voice-hearers (P-H+), and healthy controls (P-H-).

Conditioned hallucinations readily occurred in all subjects but with markedly increased frequency in those who hallucinate, regardless of psychosis status. They activated stimulus-responsive auditory cortex and a network active during clinical hallucinations. Computational modeling of perception demonstrated an increased reliance on heightened prior beliefs in voice-hearers (encoded by insula and superior temporal sulcus), regardless of psychosis status. By contrast, those with psychosis less-readily recognized changing stimulus contingencies (encoded by cerebellum and hippocampus), regardless of hallucination status.

Recently published in Science, these results may represent an objective means to distinguish people with hallucinations from those without, and, orthogonally, a need for treatment from those without. Ongoing work focuses on characterizing the predictive power of these measures in risk stratification in young people at clinical high risk of psychosis (CHR). Preliminary data suggest this approach holds promise for early detection of illness in CHR, and ongoing work aims to use these computational measures for treatment selection specific to hallucinations.

Learning Objectives

1. Participants will be able to describe perception in computational terms, as a combination of prior beliefs and incoming sensory information, and how this combination may be altered to cause hallucinations.
2. Participants will be able to identify specific computational processes that may be altered in hallucinations and psychosis, respectively, and how these findings may translate to enhanced diagnosis and personalized treatment for psychosis as it develops.

Literature References

1. Powers AR, Mathys C, Corlett PR. Pavlovian conditioning-induced hallucinations result from overweighting of perceptual priors. Science. 2017;357:596-600.

2. Powers III AR, Kelley M, Corlett PR. Hallucinations as Top-Down Effects on Perception. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2016;1:393-400.

PREDICTION OF CLINICAL DEPRESSION USING SMARTPHONE SENSORY DATA

Jayesh Kamath[1], *Jinbo Bi[2], Alexander Russel[2], Bing Wang[2]*

[1]University of Connecticut Health Center, [2]University of Connecticut

Abstract: Background: Depression questionnaires such as the Patient Health Questionnaire (PHQ-9) partially rely on behavioral data to diagnose and monitor clinical depression. Behavioral patterns can be detected by the large complement of sensors available on mobile phones including the global positioning systems (GPS) and accelerometers. Furthermore, mobile phones are ubiquitous, especially among college students. The objective of the present study is to investigate if sensory data collected from smart phones can predict depression symptomatology in a group of college participants.
Methods: A smartphone sensing app, called LifeRhythm was developed by the study team for both iOS and Android platforms. The app collected location and activity information via sensors available on the phones. A total of 81 college participants were recruited to install the app on their own smart phones over a 8 month study period. At study initiation, all participants underwent assessment by a study clinician to determine their study eligibility. They were also assessed using a Diagnostic Statistical Manual-based interview and PHQ-9 evaluation to classify them into "depressed" or "non-depressed/control" category. Three sets of data were collected during participant's study participation: Data collected by the LifeRhythm app, PHQ-9 questionnaire completed electronically by the participant very two weeks on their smart phones, and clinical assessments conducted by the study clinician on a monthly basis (for participants in the "depressed" category). Behavioral features were developed and extracted from the GPS location and phone usage data.
Results: Of the total 88 participants, 62 were iPhone users and 26 were Android phone users. A total of 18 participants were categorized as depressed and 70 were categorized as non-depressed controls. Three types of features were extracted from the data gathered by the LifeRhythm app: Features based on raw GPS data- location variance, time spent in moving, total distance, average moving speed; Features based on location clusters- variability of time spent at different locations called entropy, normalized entropy (entropy divided by the number of unique clusters), and time spent at home; Features based on activity data i.e. stationary vs non-stationary states (e.g. walking, running). Correlational analyses were conducted between the smartphone data-based features and PHQ-9 scores. The preliminary analyses of the Android data indicate the entropy and number of unique locations showed a statistically significant correlation ($p < 0.05$) with the PHQ-9 scores. Differences were noted between the correlational analyses of the Android vs iPhone data with PHQ-9 scores. Differences were also noted between the data gathered between three sets of participants in the depressed category in relation to their PHQ-9 scores: consistently high PHQ-9 scores, fluctuating PHQ-9 scores, consistently low PHQ-9 scores (in remission). Results for these will be presented and discussed in a descriptive/graphical manner.
Conclusions: This is the first study of its kind that collected smartphone based data together with clinical ground-truth to investigate depression on both iOS and Android platforms and for

a longer period. Study results suggest that behavioral data collected using the LifeRhythm app can predict and monitor clinical depression with good accuracy. The multi-feature regression model and algorithm developed by our study team further improved accuracy compared to the single feature models. Diagnosis and monitoring of clinical depression may be significantly enhanced by combining smart phone-based behavioral data with standard clinical assessments and PHQ-9 scores.

Learning Objectives

1. Describe an innovative mobile health (m-Health) based tool for prediction of clinical depression.
2. Delineate specific features of smart phone-based sensory data that correlate with depression symptomatology in clinical setting.

Literature References

1. Marzano L, Bardill A, Fields B, Herd K, Veale D, Grey N, Moran P. The application of mHealth to mental health: opportunities and challenges. Lancet Psychiatry 2015; 2(10):942-8.
2. Glenn T, Monteith S. New measures of mental state and behavior based on data collected from sensors, smartphones, and the Internet. Curr Psychiatry Rep 2014; 16(12):523.

ASSESSMENT OF IADL FUNCTIONING IN INDIVIDUALS WITH SUBJECTIVE COGNITIVE COMPLAINTS USING THE VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT TOOL (VRFCAT)

Alexandra Atkins[1], *Anzalee Khan[2], Kathleen Welsh-Bohmer[3], Brenda Plassman[3], Adam Vaughan[1], Dañela Balentin[1], Ioan Stroescu[1], Richard S.E. Keefe[4]*

[1]NeuroCog Trials, [2]NeuroCog Trials, Nathan S. Kline Institute, Manhattan Psychiatric Center, [3]Duke University Medical Center, [4]Duke University Medical Center, NeuroCog Trials

Abstract: Background: Increasing interest in clinical trials for Alzheimer's disease prevention and early intervention highlights the need for tools that are performance-based and sensitive to subtle deficits in instrumental activities in daily living (iADL) in healthier, non-demented individuals

The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) is a performance-based assessment of iADL functioning that assesses a participant's ability to complete instrumental activities (called objectives) associated with a shopping trip. In previous studies, the VRFCAT has demonstrated strong psychometric properties and shown sensitivity to declines in healthy aging and deficits in schizophrenia. Key outcome measures for the VRFCAT include total time to complete all objectives as well as individual objective times and error rates.

We present new findings from an ongoing study to collect census-matched normative data in 650 healthy individuals and 60 individuals with subjective cognitive complaints.

Methods: Data currently includes 499 participants, including 229 healthy young adults (YA, <55 years), 227 healthy older adults (hOA, ≥55 years), and 43 older adults with subjective cognitive complaints (scOAs, ≥55 years). Older adults with cognitive complaints were classified as such based on total scores of ≥ 4 on the self-reported Mail-In Cognitive Function Screening Instrument and MCFSI

In addition to the VRFCAT, participants were evaluated with standard cognitive assessments including the Montreal Cognitive Assessment (MoCA), Trail Making Part B, Logical Memory I and II, and the Brief Assessment of Cognition (BAC App). Participants ≥ 55 years of age completed the MCFSI. Those with cognitive complaints were asked to provide an informant to complete the ADCS Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI).
Results: Participants with subjective cognitive decline performed significantly lower than hOAs without on all standard neurocognitive measures, indicating subjective decline was associated with objective deficits. VRFCAT total completion time, error rate and number of forced progressions all demonstrated strong sensitivity to differences between groups ($p \leq .001$). In the subjective cognitive decline group, VRFCAT performance was correlated with aspects of informant reported iADL function on the ADCS-ADL PI. First, VRFCAT completion time was positively correlated with informant reported difficulties in shopping ($r=.456$, $p<.001$). Second, VRFCAT errors were positively correlated with informant-reported difficulties in completing complex activities ($p=.38$, $p<.05$).
VRFCAT error and total time endpoints were strongly correlated with cognitive measures. In subjective cognitive decline group, MoCA scores were correlated with both VRFCAT total time ($r=-.51$, $p<.001$) and VRFCAT errors ($r=-.47$, $p<.01$). VRFCAT errors also were correlated with reduced performance on symbol coding ($p=-.35$, $p<.01$), executive functioning ($-.60$, $p<.001$) and visuospatial working memory ($r=.51$, $p<.01$). VRFCAT completion time was strongly correlated TMT-B ($r=.60$, $p<.001$), semantic fluency ($r=-.41$, $p<.01$), symbol coding ($-.55$, $p<.001$), executive functioning ($r=-.46$, $p<.001$) and visuospatial working memory ($r=-.58$, $p<.001$).
Conclusion: Results suggest the VRFCAT is sensitive to differences between healthy OAs and those with subjective cognitive complaints, and demonstrate convergence between VRFCAT findings, objective cognitive testing, and informant reports of function.

Learning Objectives

1. Understand the need for improved functional assessment in preclinical MCI/AD.
2. Gain familiarity with a novel performance-based approach to functional assessment.

Literature References

1. Atkins AS, Stroescu I, Spagnola, N Davis VG et al. Assessment of Age-Related Differences in Functional Capacity Using the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). JPAD, 2015; 2. 121-127.
2. Keefe RS, Davis VG, Atkins AS, Vaughan A, Patterson T, Narasimhan M, et al. Validation of a computerized test of functional capacity. Schizophr Res. 2016;175:90-96.

RANDOMIZED CONTROLLED TRIAL TESTING THE EFFECTIVENESS OF AN "ADAPTIVE SMART" STEPPED-CARE MULTI-MODAL TREATMENT FOR ADULTS WITH OBESITY AND BINGE EATING DISORDER

Carlos Grilo[1]

[1]*Yale University School of Medicine*

Abstract: Introduction: Although research has identified specific psychological and pharmacological approaches that are effective for treating binge eating disorder (BED), many

patients fail to derive sufficient benefit. Combining methods has generally failed to enhance outcomes and identifying moderators of treatment response to inform treatment-matching has been elusive. There exists a need for novel research designs to inform evidence-based guidelines for selecting sequential or additional treatment approaches for patients in general and especially for those who are non-responsive to initial treatments. This randomized controlled trial tested the effectiveness of an "adaptive SMART" stepped-care treatment versus behavioral weight loss (BWL) for patients with obesity and BED.

Methods: 191 patients (mean age 48, 71% female, 79% white) with BED and co-morbid obesity (mean BMI 39) were randomly assigned to 6 months of BWL (N=39) or stepped-care (N=152). Within stepped-care, patients started with BWL for one month; treatment-responders continued with BWL while non-responders switched to specialist treatment (CBT) and all stepped-care patients were additionally randomized to either anti-obesity medication or placebo (double-blind) for the remaining five months. Independent assessments were performed at baseline, during treatment, post-treatment (6 months), and 6- and 12-month follow-ups after completing treatments (through 18 months) with reliably-administered structured interviews and measures.

Results: ITT analyses of abstinence rates (zero binges/month) revealed BWL and stepped-care did not differ significantly overall at post-treatment (74% vs 64%) or 12-month follow-up (45% vs 41%). Mixed-models regression analyses of binge-eating frequency through post-treatment revealed significant time effects but that BWL and stepped-care did not differ overall; within stepped-care, however, medication was significantly superior to placebo overall and among initial non-responders switched to CBT. Mixed-models of binge-eating frequency during the 12-months after treatment revealed good maintenance that did not differ across treatments. Mixed models revealed significant % weight loss through post-treatment but BWL and stepped-care did not differ overall; within stepped-care, however, medication was significantly superior to placebo overall and among both initial responders who continued BWL and non-responders who were switched to CBT. Mixed-models during follow-up revealed significant time effects with % weight change larger at 6 than 12 months; percent weight loss at 12-month follow-up was 4% (BWL), 6% (BWL+placebo), and 7.5% (BWL+medication).

Conclusion: Overall, BWL and the "adaptive" stepped-care treatments produced significant improvements in binge-eating and weight loss that were maintained through 18 months in obese patients with BED. Anti-obesity medication enhanced outcomes with behavioral treatments within stepped-care.

Learning Objectives

1. Following the presentation, participants will be able to recognize available behavioral and anti-obesity treatments for binge eating disorder.
2. Following the presentation, participants will be able to describe expected acute and longer-term outcomes associated with behavioral weight loss and stepped-care treatment methods for binge eating disorder.

Literature References

1. Grilo CM: Psychological and behavioral treatments for binge-eating disorder. J Clin Psychiatry 2017;78(S1):20-24 https://www.ncbi.nlm.nih.gov/pubmed/28125175.
2. Grilo CM, Reas DL, Mitchell JE: Combining pharmacological and psychological treatments for binge eating disorder: current status, limitations, and future directions. Cur Psychiatry Rep 2016;18(6):55 https://www.ncbi.nlm.nih.gov/pubmed/27086316.

Individual Research Report Session: Studies in MDD: New Approaches and Treatments*
4:15 p.m. - 5:30 p.m.

IDENTIFYING CHARACTERISTICS OF PLACEBO RESPONDERS IN MAJOR DEPRESSION FROM THE EMBARC STUDY

Madhukar Trivedi[1], Charles South[1], Manish Jha[2], Augustus Rush[3], Benji Kurian[1], Mary Phillips[4], Diego Pizzagalli[5], Joseph Trombello[1], Maria Oquendo[6], Crystal Cooper[1], Gerard Bruder[7], Patrick McGrath[8], Ramin Parsey[9], Myrna Weissman[10], Maurizio Fava[5]

[1]UT Southwestern Medical Center, [2]UT Southwestern, [3]National University of Singapore, [4]University of Pittsburgh School of Medicine, [5]Massachusetts General Hospital, [6]University of Pennsylvania Perelman School of Medicine, [7]New York State Psychiatric Institute, College of Physicians and Surgeons, [8]New York State Psychiatric Institute, [9]Stony Brook University, [10]Columbia University

Abstract: Background: One in three patients with major depressive disorder (MDD) report symptomatic improvement with placebo in clinical trials. Strategies to mitigate the effect of rising placebo response rates have focused on modifying study design with limited success. Clinical trial efficiency can be improved and unnecessary medication trials avoided by identifying and excluding or controlling for individuals with high likelihood of responding to placebo.

Methods: Data for this report are based on participants of the Establishing Moderators and Biosignatures for Antidepressant Response in Clinical Care (EMBARC) trial who were assigned to the placebo arm (n=141). The elastic net was used to evaluate a total of 283 baseline clinical, behavioral, imaging, and electrophysiological variables in order to identify the most robust set of features that predicted depression severity at week 8 in 100 imputed datasets. Variables that were retained by the elastic net in at least 50% of the imputed datasets were then used in a Bayesian multiple linear regression model to simultaneously predict depression symptom level at exit, the probability of response, and the probability of remission.

Results: Lower baseline depression severity, younger age, absence of melancholic features or history of physical abuse, less anxious arousal, anhedonia and neuroticism, and higher average theta current density in the rostral anterior cingulate predicted higher likelihood of improvement with placebo. The Bayesian model incorporating variables predictive of placebo response was able to predict remission and response with a relatively high degree of accuracy (AUC values of 0.76 and 0.73, respectively), and an interactive calculator using the model was developed.

Conclusion: Easy to measure clinical, behavioral and electrophysiological assessments can be used to identify responders to placebo with high degree of accuracy. Development of the calculator based on these findings can be used in the screening process to reduce placebo response rates.

Learning Objectives

1. Understand the predictive nature of a breadth of demographic, clinical, behavioral, imaging, and electrophysiological markers on placebo response in depression.
2. Utilize and interpret a calculator that can be used by clinicians and researchers to screen for potential placebo responders by estimating the likelihood of remission and response.

Literature References

1. Enck P, Bingel U, Schedlowski M, Rief W: The placebo response in medicine: minimize, maximize or personalize?. Nature reviews Drug discovery. 2013 Mar;12(3):191.
2. Trivedi MH, McGrath PJ, Fava M, et al: Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. Journal of psychiatric research. 2016 Jul 1;78:11-23.

HAVE TREATMENT STUDIES OF DEPRESSION BECOME EVEN LESS GENERALIZABLE? APPLYING THE INCLUSION AND EXCLUSION CRITERIA IN PLACEBO CONTROLLED ANTIDEPRESSANT EFFICACY TRIALS PUBLISHED OVER 20 YEARS TO A CLINICAL SAMPLE

Mark Zimmerman[1], *Caroline Balling*[2]

[1]*Brown University,* [2]*Rhode Island Hospital*

Abstract: Introduction: We previously conducted a review of the psychiatric inclusion/exclusion criteria in placebo-controlled AETs published from January, 1995 through December, 2014. We compared the criteria of studies published during the past 5 years (2010-2014) to those of the prior 15 years (1995-2009) and found that the inclusion/exclusion criteria for AETs narrowed in the studies of the more recent five years thereby suggesting that AETs may be even less generalizable than they were previously. In this presentation we apply the criteria used in these studies to a large sample of depressed outpatients to examine the actual impact of the change on generalizability.

Methods: One thousand two hundred seventy-one patients with a principal diagnosis of major depressive disorder were interviewed with semi-structured interviews. The psychiatric inclusion/exclusion criteria of 122 placebo-controlled AETs were applied to the patients.

Results: Across all studies, the percentage of patients that would have been excluded ranged from 44.4% to 99.4% (mean=86.0%). The percentage of patients that would have been excluded was significantly greater in the studies published in 2010-2104 compared to the studies published during the prior 15 years (93.6% vs. 83.9%, $p<.001$).

Discussion: The results expand prior findings that only a minority of depressed patients seen in clinical practice are likely to be eligible for most AETs, thereby raising questions about the generalizability of AETs to patients treated in the real world. Moreover, generalizability was significantly lower in more recently conducted studies.

Learning Objectives

1. To appreciate the extent to which patients seen in clinical practice are not included in studies of the efficacy of antidepressants.
2. To appreciate that antidepressant efficacy trials have become less generalizable over time.

Literature References

1. Zimmerman, M., Clark, H.L., Multach, M.D., Walsh, E, .Rosenstein, L.K., & Gazarian, D. Have Treatment Studies of Depression Become Even Less Generalizable? A Review of the Inclusion and Exclusion Criteria in Placebo Controlled Antidepressant Efficacy Trials Published During the Past 20 Years. Mayo Clinic Proceedings, 2015, 90, 1180-1186.

2. Posternak, M.A., Zimmerman, M., Miller, I., & Keitner, G. A reevaluation of the exclusion criteria used in antidepressant efficacy trials. American Journal of Psychiatry, 2002, 159, 191-200.

AGE, TREATMENT AND BASELINE SEVERITY AS FACTORS IN SUICIDAL BEHAVIOR IN RANDOMIZED PLACEBO-CONTROLLED TRIALS IN MAJOR DEPRESSIVE DISORDER

Marc Stone[1], *Brian Miller[2], Shamir Kalaria[3], Kyle Richardville[4]*

[1]FDA/CDER/DPP, [2]Georgetown University, [3]University of Maryland, [4]University of North Carolina

Abstract: The Division of Psychiatry Products at FDA has constructed a database of all randomized placebo-controlled trials of antidepressants in the treatment of Major Depressive Disorder submitted between 1979 and 2016. These 228 studies enrolled 73,178 subjects; 66.3% were assigned to one of 21 antidepressant drugs and 33.7% to placebo. The overall incidence of suicidal behavior was 0.28% in both placebo and active drug groups. Incidence was highest (0.59%) before 1990, and lowest between 1995 and 2000 (0.20%). Risk of suicidal behavior was strongly related to severity of depression at baseline. The incidence of suicidal behavior was 0.06% among subjects with the equivalent of a HAMD17 score of 20 or less and 0.83% among subjects with a score equivalent to 30 or more. Incidence declined with age in both treatment groups but the gradient was steeper among subjects receiving active drug, resulting in a higher risk in active drug subjects through age 40 and a higher risk with placebo in older subjects.

Learning Objectives

1. Understand the risk of emergent suicidal behavior in short-term placebo-controlled trials in Major Depressive Disorder.
2. understand the interaction of age, depression severity and drug treatment in affecting the risk of suicidal behavior in short-term MDD studies.

Literature References

1. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G: Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880.
2. Hammad T, Laughren T, Racoosin JA: Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332-9.

SAGE-217 A FIRST IN CLASS GABAA RECEPTOR POSITIVE ALLOSTERIC MODULATOR BEING DEVELOPED FOR MAJOR DEPRESSIVE DISORDER: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PHASE II PLACEBO-CONTROLLED TRIAL

Handan Gunduz-Bruce[1], Christopher Silber[1], Anthony J. Rothschild[2], Robert Riesenberg[3], Abdul Sankoh[1], Haihong Li[1], Ella Li[1], Charles Zorumski[4], David Rubinow[5], Steven Paul[1], Jeffrey Jonas[1], James Doherty[1], Stephen Kanes[1]

[1]Sage Therapeutics, [2]University of Massachusetts Medical School and University of Massachusetts Memorial Health Care, [3]Atlanta Center for Medical Research, [4]Washington University, St. Louis, [5]University of North Carolina

Abstract: Background: Major depressive disorder (MDD) is a disabling and potentially life-threatening condition. GABAergic signaling has been linked to the etiology of MDD and presents an opportunity for medication development with a novel mechanism of action. SAGE-217 is an orally active, positive allosteric modulator (PAM) of synaptic and extrasynaptic GABAA receptors that was well-tolerated and showed anti-depressive effects in an open label study in subjects with MDD. This is the first double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of SAGE-217 in subjects with moderate to severe MDD.

Methods: This multicenter study included 89 subjects of both sexes, ages 18-65, with a diagnosis of MDD and a Hamilton Rating Scale for Depression (HAM-D) total score ≥22. Subjects were randomized 1:1 to receive a nightly dose of SAGE-217 Capsule (30 mg) or placebo on Days 1-14, followed by 4 weeks off treatment. The primary endpoint was the reduction in depressive symptoms, compared to placebo, as assessed by the change in the 17-item HAM-D total score from baseline to Day 15. Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A) and Clinical Global Impression-Improvement (CGI-I) were also examined. Pharmacokinetic data were collected. Adverse events (AEs) and other safety measures were obtained through Day 42.

Results: The SAGE-217 group showed a greater mean reduction from baseline in HAM-D total score compared to the placebo group at Day 15 (17.6 for SAGE-217 vs 10.7 for placebo; $p<0.0001$). Statistically significant improvements in HAM-D score vs placebo were first observed on Day 2 ($p=0.0223$) and were present on Days 15 ($p<0.0001$) and 28 ($p=0.0243$). The MADRS total score also showed a greater mean reduction from baseline in the SAGE-217 group vs placebo group at Day 15 ($p=0.0021$). The significant reduction in MADRS scores vs placebo was also maintained through Day 28. Statistically significant mean improvements in the SAGE-217 group vs placebo were also observed for the HAM-A and CGI-I endpoints at Day 15. There were no deaths, serious or severe AEs. There were two discontinuations in the SAGE-217 group due to AEs. The most common AEs (at least 5%) in the SAGE-217 group were headache, nausea, dizziness, and somnolence.

Conclusions: This is the first placebo-controlled, randomized clinical trial to evaluate the efficacy and safety of the oral neuroactive steroid SAGE-217, a GABAA receptor PAM, in adult male and female subjects with moderate to severe MDD. Administration of SAGE-217 for 14 days resulted in robust and rapid mean reductions in depressive symptoms that were sustained over the study period. SAGE-217 was generally well tolerated. These results provide strong evidence that positive allosteric modulation of GABAA receptors is a viable path for investigation in developing treatments for MDD and support further development of SAGE-217 for this indication.

Learning Objectives

1. Understand the role of GABA signaling dysfunction in major depressive disorder.
2. Understand the potential role and on-going development of neuroactive steroid positive allosteric modulators of GABA-A receptors as a novel therapeutic mechanism in major depressive disorder.

Literature References

1. Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry 2011;16(4):383-406. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3412149/.

2. Kanes S, Colquhoun H, Gunduz-Bruce H et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. The Lancet 2017; 390(10093):480-489.http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31264-3/fulltext.

Wednesday, May 30, 2018

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

REGULATORY PLENARY: AUTISM SPECTRUM DISORDER

John Newcomer, Charles E. Schmidt College of Medicine, Florida Atlantic University

Overall Abstract: This year's Regulatory Plenary will focus on FDA and EMA initiatives related to Autism Spectrum Disorder (ASD) and other neurodevelopmental disorders. FDA will discuss last year's Patient Focused Drug Development meeting on ASD and the recently published Voice of the Patient report. FDA will also describe collaborative efforts between FDA and EMA to align regulatory advice related to ASD and other neurodevelopmental disorders. EMA will provide an update on EU-AIMS (the Innovative Medicines Initiative project exploring potential biomarkers in ASD). EMA will also discuss the strengths and limitations of their Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder.

AUTISM SPECTRUM DISORDER

Tiffany Farchione, US Food and Drug Administration
Valentina Mantua, AIFA

Abstract: This year's Regulatory Plenary will focus on FDA and EMA initiatives related to Autism Spectrum Disorder (ASD) and other neurodevelopmental disorders. FDA will discuss last year's Patient Focused Drug Development meeting on ASD and the recently published Voice of the Patient report. FDA will also describe collaborative efforts between FDA and EMA to align regulatory advice related to ASD and other neurodevelopmental disorders. EMA will provide an update on EU-AIMS (the Innovative Medicines Initiative project exploring potential biomarkers in ASD). EMA will also discuss the strengths and limitations of their Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder.

Learning Objectives

1. Understand the features of ASD that individuals with ASD consider important targets for treatment.
2. Learn the EU regulatory framework for the development of products for Autism Spectrum Disorder (ASD).

Literature References

1. https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM594722.pdf .
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/11/WC500238886.pdf.

ASCP Awards Ceremony and ASCP Lifetime Awardee Talk
10:15 a.m. - 11:15 a.m.

REFLECTIONS ON THE DEVELOPMENT OF GLUTAMATE-BASED ANTIDEPRESSANTS

Phil Skolnick, Opiant Pharmaceuticals, Inc.

Abstract: Three decades after the first hypothesis driven study demonstrating antidepressant-like effects of N-methyl-D-aspartate (NMDA) antagonists, esketamine (the S-enantiomer of ketamine, an ion channel blocker) and rapastinel (an NMDA receptor linked glycine site partial agonist) are in late stage development for treatment resistant depression. The dramatic antidepressant effects produced by intravenous infusion of subanesthetic doses of ketamine, taken together with an emerging understanding of glutamatergic signaling, suggests the glutamatergic synapse contains multiple targets for antidepressant development. Despite some modest efficacy signals emerging from large, well-controlled clinical studies with other glutamate-based drugs (ranging from lanicemine, an NMDA ion channel blocker, to basmiglurant, a negative allosteric modulator at mGluR5 receptors), the rapid and robust effects of ketamine in treatment resistant depression could be viewed as an apparent anomaly rather than a characteristic of this drug class. In this presentation, I will review preclinical and clinical data with an eye toward features which potentially distinguish ketamine from other glutamate-based agents, and reflect on the viability of the glutamatergic synapse as a target for future drug development.

Learning Objectives

1. Understand the bases for developing glutamate-antidepressants, and why this approach offers advantages to current amine-based agents.
2. Understand the different types of glutamate-based antidepressants currently in development.

Literature References

1. Garay R, Zarate CA, Cavero I, et al: The development of glutamate-based antidepressants is taking longer than expected. Drug Disc. Today 2018 (March 1); pii: S1359-6446(17)30332-X. doi: 10.1016/j.drudis.2018.02.006.
2. Skolnick P, Popik P, Trullas R: Glutamate-based antidepressants: 20 years on. Trends Pharmacol Sci. 2009; 30: 563-569
3. Trullas, R, Skolnick P: Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur. J. Pharmacol. 1990; 190: 11-21.

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

NEW PERSPECTIVES ON TREATMENT RESISTANT SCHIZOPHRENIA (TRS)

John Kane, The Zucker Hillside Hospital

Overall Abstract: Treatment resistance occurs in up to 30% of individuals with schizophrenia and represents a major unmet need. It is associated with greater disability, morbidity, mortality and societal burden. Most individuals with schizophrenia, however, respond well to

antipsychotic medication (in terms of positive symptoms) at early stages of the illness, with only 10-15% evidencing treatment resistance from illness onset. The factors involved in the subsequent development of resistance to antipsychotic treatment are not well understood. The panel will address this challenge from a variety of clinical and research relevant perspectives
Bruce Kinon will discuss contrasting patient segments with regard to onset of TRS (early vs later phase illness), clinical symptoms upon presentation, illness prognosis and predictors of response/non-response (e.g. the predictive power of lack of minimal response after two weeks of acute treatment, which has now been studied in an extensive series of trials). Although TRS has been viewed from genetic, neuroimaging and phenomenological perspectives, many unanswered questions remain.
Jose M. Rubio will discuss Breakthrough on Antipsychotic Maintenance Medication (BAMM) in individuals adherent to long acting injectable (LAI) formulations. This represents an ideal paradigm to study the mechanisms involved in the failure to maintain response to antipsychotic maintenance medication, removing the potential confounder of medication non-adherence. The degree to which the development of BAMM is related to the development of resistance to the amelioration of psychotic symptoms by antipsychotic drugs has received little attention to date. He will present data on the cumulative incidence and independent predictors of BAMM from 2 separate datasets. The first involves individual participant level meta-analysis of industry sponsored relapse prevention trials for LAI formulations including 8 treatment arms with a total of 1860 participants. The second dataset is a real-world naturalistic cohort of 220 patients with psychosis on stable LAI treatment that were followed for up to 5 years. Additionally, he will present observational data regarding the current treatment strategies for the management of BAMM and their relative effectiveness in a clinical sample. Finally, we will review the overlap in incidence and predictors between BAMM and treatment resistant schizophrenia.
John M. Kane will discuss the design and conduct of clinical trials for TRS and review current data on the efficacy and effectiveness of clozapine within that context. Despite almost thirty years passing since the FDA approval of clozapine for TRS, a recent well-conducted meta-analysis concluded “At present, insufficient blinded evidence exists on which antipsychotic is more efficacious for patients with treatment-resistant schizophrenia.” The recent Treatment Response and Resistance in Psychosis (TRRIP) Working Group identified 42 clinical trials involving putative TRS and found that 21 (50%) of them did not utilize operation criteria to define treatment resistance and only two used the same criteria. Enormous problems remain in the quality of available evidence and it is embarrassing to the field to still have this degree of uncertainty regarding clozapine after three decades.

Learning Objectives

1. Become familiar with the phenomenological correlates of treatment resistant schizophrenia.
2. Assume breakthrough psychosis as a paradigm to study the development of treatment resistant schizophrenia.
3. Identify the challenges of clinical trials in treatment resistant schizophrenia and their implications.

THE GROUP OF TREATMENT RESISTANT SCHIZOPHRENIAS?
Bruce Kinon, Lundbeck

Individual Abstract: Significant heterogeneity exists among those schizophrenia patient segments that commonly share a resistance to currently available antipsychotic drug treatment. This heterogeneity is most prominently reflected in patients demonstrating treatment resistance early in their disease course (i.e. early-in-disease Treatment Resistant Schizophrenia (TRS); ED TRS) as compared to those developing treatment resistance later in their disease (i.e. late-in-disease TRS; LD TRS) presumably after having enjoyed treatment response earlier in their illness. Furthermore, heterogeneity among TRS patient segments is evidenced by the significant proportion of patients who differentiate on whether or not they may improve with clozapine (CLZ), the only approved treatment for TRS.

Since treatment resistance as presently defined infers resistance in most part to dopamine D2 receptor (DAD2R) antagonism in relevant CNS loci, the pathology responsible for ED TRS may reflect a neurodevelopmental non-dopaminergic abnormality beyond the DAD2R as contrasted with LD TRS which may result from a neuroadaptive or neurodegenerative loss of therapeutic response to DAD2R antagonism. Trait (e.g. genetic; neuro-structural; CNS connectivity; etc.) as well as state (e.g. epigenetic; prevention/delay of conversion to psychosis; time on treatment; cumulative time in psychosis; comorbid disease; etc.) factors may determine the various patient trajectories that may ultimately lead to TRS. Characterization of patient segments that may comprise TRS could possibly reflect a diverse neurobiological sub-classification of TRS or conversely reflect outliers on a continuum of disease outcome severity that characterizes schizophrenia in general.

The concept of heterogeneity in TRS will be explored through review of patient segments whose disease morbidity is differentiated by:

- Risk factors associated with development of schizophrenia in the general population as well as in clinical high risk cohorts;
- Early response/non-response as a predictor of outcome to a therapeutic antipsychotic trial in acute symptomatic schizophrenia;
- Onset of TRS in longitudinal schizophrenia disease course
- Clinical symptoms upon TRS presentation;
- Response/non-response to CLZ in TRS

Available data including premorbid and comorbid disorders, psychosocial functioning, resource utilization, genetics, and neuroimaging that may characterize the identified heterogeneous patient segments will be reviewed for their association with the enduring and persistent distal disease state of TRS.

A better understanding of patient segments that may comprise “the group of TRS schizophrenias” may enable the development of targeted therapeutics for those patients most likely to respond to specific treatments.

Learning Objectives

1. To become familiar with and recognize the various clinical presentations of TRS.
2. To understand how the heterogeneity within TRS patient segments may better inform the development of new treatments for TRS.

Literature References

1. Lally J, Ajnakina O, Di Forti M, Trotta A, Demjaha A, Kolliakou A, Mondelli V, Reis Marques T, Pariante C, Dazzan P, Shergil SS, Howes OD, David AS, MacCabe JH, Gaughran F, Murray RM. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. Psychological Medicine 2016;46(15):3231-3240.

2. Gillespie AL, Samanaite R, Mill J, Egerton A, MacCabe JH. Is Treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? a systematic review. BMC Psychiatry 2017; 17:12. doi.org/10.1186/s12888-016-1177-y.

IS THERE CONTINUITY BETWEEN BREAKTHROUGH ON ANTIPSYCHOTIC MAINTENANCE MEDICATION (BAMM) AND TREATMENT RESISTANT SCHIZOPHRENIA (TRS)? NEW OPPORTUNITIES FOR IDENTIFICATION AND INTERVENTION

Jose Rubio, Hofstra NS-LIJ School of Medicine

Individual Abstract: Treatment resistance occurs in up to 30% of individuals with schizophrenia. It is associated with greater disability, morbidity, mortality and societal burden. A sizeable proportion of individuals with schizophrenia however respond to antipsychotic medication at earlier stages of the illness before they become treatment resistant. The factors involved in the development of resistance to antipsychotic treatment are not well understood. The study of psychosis Breakthrough on Antipsychotic Maintenance Medication (BAMM) in individuals adherent with long acting injectable (LAI) formulations represents an ideal paradigm to study the mechanisms involved in the failure to maintain response to antipsychotic maintenance medication, removing the potential confounder of medication non-adherence. The degree to which the development of BAMM is related to the development of resistance to the amelioration of psychotic symptoms by antipsychotic drugs has received little attention to date.

We will present data on the cumulative incidence and independent predictors of BAMM from 2 separate datasets. The first involves individual participant level meta-analysis of industry sponsored relapse prevention trials for LAI formulations including 8 treatment arms with a total of 1860 participants. The second dataset is a real-world naturalistic cohort of 220 patients with psychosis on stable LAI treatment that were followed for up to 5 years. Additionally, we will present observational data regarding the current treatment strategies for the management of BAMM and their relative effectiveness in a clinical sample. Finally, we will review the overlap in incidence and predictors between BAMM and treatment resistant schizophrenia.

Learning Objectives

1. Become familiar with the concept of Breakthrough on Antipsychotic Maintenance Medication (BAMM) as a phenomenon in the treatment course of schizophrenia in general, and within the timeline of the development of Treatment Resistant Schizophrenia (TRS) in particular.
2. Compare the clinical predictors of Breakthrough on Antipsychotic Maintenance Medication (BAMM) and Treatment Resistant Schizophrenia (TRS).

Literature References

1. Rubio JM, Kane JM. Psychosis breakthrough on antipsychotic maintenance medication (BAMM): what can we learn? NPJ Schizophr. 2017 Oct 11;3(1):36. doi: 10.1038/s41537-017-0039-z.
2. Alphs L, Nasrallah HA, Bossie CA, Fu DJ, Gopal S, Hough D, Turkoz I. Factors associated with relapse in schizophrenia despite adherence to long-acting injectable antipsychotic therapy. Int Clin Psychopharmacol. 2016 Jul;31(4):202-9.

CLINICAL TRIALS IN TRS: THE GOOD, THE BAD AND THE UGLY

John Kane, The Zucker Hillside Hospital

Individual Abstract: Despite the fact that at least 30% of patients with schizophrenia would qualify at some point in their illness as treatment resistant our knowledge of and ability to treat this phenomenon remains limited. Although clozapine continues to be the only medication with an FDA approved indication for treatment resistance, a recent well-conducted meta-analysis concluded "at present insufficient blinded evidence exists on which antipsychotic is more efficacious for patients with treatment-resistant schizophrenia. In addition, in a review of 42 clinical trials involving putative treatment resistant schizophrenia (TRS) the Treatment Response and Resistance in Psychosis Working Group reported that only 21 (50%) used operational criteria for TRS and only two used the same criteria.
This presentation will discuss important design features to be considered in the study of treatments for TRS, and review pros and cons as well as the feasibility of such methodologies. An additional challenge is the management of those patients who derive insufficient benefit from clozapine treatment. This presentation will provide data utilizing different criteria and thresholds for clozapine response and how these impact the rate of clozapine resistance found in a sample of 300 clozapine-treated patients.
Overall, the presentation will provide important guidelines to clinicians and researchers alike on the nature and limitations of existing data on TRS.

Learning Objectives

1. To educate attendees about research design and methodology in clinical trials for treatment resistant schizophrenia.
2. To review different strategies for defining and ascertaining treatment resistance.
3.

Literature References

1. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, Bloomfield MA, Bressan RA, Buchanan RW, Carpenter WT, Castle DJ, Citrome L, Daskalakis ZJ, Davidson M, Drake RJ, Dursun S, Ebdrup BH, Elkis H, Falkai P, Fleischacker WW, Gadelha A, Gaughran F, Glenthøj BY, Graff-Guerrero A, Hallak JE, Honer WG, Kennedy J, Kinon BJ, Lawrie SM, Lee J, Leweke FM, MacCabe JH, McNabb CB, Meltzer H, Möller HJ, Nakajima S, Pantelis C, Reis Marques T, Remington G, Rossell SL, Russell BR, Siu CO, Suzuki T, Sommer IE, Taylor D, Thomas N, Üçok A, Umbricht D, Walters JT, Kane JM, Correll CU. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology.Am J Psychiatry. 2017 Mar 1;174(3):216-229.
2. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, Leucht S. JAMA Psychiatry 2016 Mar;73(3):199-210.

LONG-TERM MEDICATION FOR AXIS I DISORDERS: LIFETIME TREATMENT OR NOT?*

Ira Glick, Stanford University School of Medicine

Overall Abstract: Introduction: While there is extensive evidence supporting efficacy of medications for major depressive disorder (MDD), bipolar disorder (BD), anxiety disorder (AD) and schizophrenia, the question of how long to stay on medication after an acute episode

continues to be debated. This panel will present the long-term outcome data to speak to that question.
Methods: Global outcome, symptoms, and functional data from long-term (>10 years) studies of patients with the above four disorders will be presented by Dr. Post (BD), Dr. Trivedi (MDD), Dr. Salzman (anxiety disorders), and Dr. Glick (schizophrenia) on data on effects of discontinuation as well as large-scale, real-world trials will be presented.
Results: All studies show a strong effect of a positive correlation of adequate medication adherence and improving outcomes. Lack of medications almost always resulted in poor outcomes, often disastrous. The data are strongest that repeated drug discontinuations and associated relapses can drive treatment refractoriness. We will discuss the utility of direct recommendations for long-term, vs indefinite, vs lifetime treatment. We will also discuss predictors of long-term outcome to assist clinical decision making.
Summary and Conclusion: Results strongly suggest, not prove, better outcome is strongly associated with higher medication adherence. Such therapeutic approaches are readily accepted in the treatment of hypertension, diabetes mellitus, etc, but often not accepted or recommended in psychiatric illness. The strength of the database and rationale for the recommendation across the different illnesses will be discussed.

Learning Objectives

1. Results of long term medication treatment of schizophrenia, major depressive disorder, bipolar disorder, and anxiety disorder.

2. Guidelines for lifetime treatment of schizophrenia, major depressive disorder, bipolar disorder, and anxiety disorder.

LONG TERM PROPHYLAXIS AFTER A FIRST MANIC EPISODE

Robert Post, Bipolar Collaborative Network

Individual Abstract: Background: There is increasing evidence that bipolar illness can run a progressively deteriorating course if not adequately treated. This can include: episode acceleration, accumulation of psychiatric and medical comorbidities, cognitive dysfunction, disability, treatment refractoriness, and loss of decades of life expectancy, even more from cardiovascular disease than from suicide. Given this ominous and all-too-common course and outcome, we review the data supporting new treatment principles and guidelines.
Methods: We review the literature about the onset of prophylactic treatment and evidence for and against the recommendation for lifetime prophylaxis.
Results: New evidence in the literature has changed the recommendation for starting prophylaxis after a first to third manic episode, to comprehensive multimodal treatment after a first manic episode, preferably including lithium. This is based on the data of: Kessing et al 2013 of superior long term (6 year outcomes) after 2 years of randomization to a specialty clinic vs TAU; Yatham et al 2017 that cognition recovers after a first mania only if there are no further episodes in the next year; and Berk et al 2017 of the superiority of 1 year on randomized lithium vs quetiapine on virtually all measures. In multiple studies in the literature, relapse rates approach 90% after 1-3 years even with guideline-based treatment; and relapses are more rapid with treatment discontinuation.
Conclusion: Given these data on illness progression and high risk of relapse, the recommendation for lifetime prophylaxis is strongly supported. Moreover, there should be a

new paradigm of intensive pharmacotherapy, psychotherapy, psychoeducation, and mood monitoring after a first manic episode, preferably involving lithium.

Learning Objectives

1. Review data on the importance of instituting prophylactic treatment after the first manic episode.
2. Review ways of preventing epigenetic-based sensitization effects driving illness progression in bipolar disorder.

Literature References

1. Post, R. M. (2017). The New News About Lithium: An Underutilized Treatment in The United States. Neuropsychopharmacology. doi:10.1038/npp.2017.238.
2. Post, R. M. (2017). New Perspectives on the Course and Treatment of Bipolar Disorder. Minerva Med, 58(1), 40-53.

MAINTENANCE TREATMENT FOR DEPRESSION: TO DISCONTINUE OR NOT

Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: Background: Depression is a common, serious, chronic or recurring illness that is life-long in the vast majority of patients affected. Only a third of individuals affected with depression achieve remission with any given antidepressant. Over 50% experience a relapse or recurrence of depression, commonly within the first six to twelve months of remission. Almost all placebo-controlled antidepressant discontinuation trials demonstrate that continuing antidepressants reduces relapse and recurrence rates. Remarkably, in a 25-year FDA perspective involving a meta-analysis of 15 maintenance studies comparing continued medication versus switch to placebo after acute response, continued medication led to a 52% reduction in relapse rates compared to placebo. In fact, all 15 studies demonstrated superiority of medication maintenance over placebo (Borges et al., 2014). Since the vast majority of patients are managed in primary care, UT Southwestern's Center for Depression Research and Clinical Care developed technology (VitalSign6) to assist primary care providers with universal screening and algorithm-guided measurement based care for depression. This presentation will examine the results of these long-term trials, as well present new data from the long-term outcomes for patients identified in the UT Southwestern cohort.
Method: VitalSign6 was launched in 2014, and fourteen clinics participated in training and implementation of the program. Clinic staff and providers were trained about depression, course of illness, and acute and maintenance treatment. In addition, providers receive ongoing decision support through the VitalSign6 application and consultation with psychiatrists and psychologists at UT Southwestern. Universal screening is accomplished via a VitalSign6 iPad. Those who screen positive receive further assessments of depression (PHQ-9) and other associated factors, such as anxiety, alcohol/substance use, mania, pain, and functioning through the application. Treatment is managed by the primary care provider using measurement-based care in which patients are assessed for changes in each of the above domains at follow-up visits.
Results: Over 32,000 patients were screened for depression, of whom 3,112 received a depression diagnosis and began antidepressant treatment. Of these, 691 (22%) continued in follow-up with their primary care provider for at least one year. Mean age of the sample was 45.3 ±13.2 years, and approximately half of the patients (49.1%) were from low-income or charity clinics. Mean PHQ-9 score at screening was 16.1 ±5.3. Participants attended an average of 6.5 ±5.0 visits, and remained in follow-up for 504.9 ±144.4 days. Simple linear regression

predicting PHQ-9 score using visit was significant (f1,4232=64.1, p<.001), with PHQ-9 scores decreasing over time (β=-0.165, p<.001). At the final visit, 81.4% were still on pharmacological treatment. Additional data will be presented on course of illness and outcomes for associated symptoms (anxiety, alcohol/substance use, mania, pain, and functioning).
Conclusions: Unlike most medical illnesses such as diabetes and cardiovascular illnesses, limited data are available on outcomes of long-term treatment for depression. These preliminary data demonstrate that while it is challenging to maintain patients in treatment, those who continue to be monitored show improvements over time.

Learning Objectives

1. To describe our current knowledge about implementation of depression screening and measurement based care in primary care settings.
2. To review research on relapse prevention of depression in adults, and to explore the long-term depression treatment outcomes in primary care settings.

Literature References

1. Borges S, Chen YF, Laughren TP, Temple R, Patel HD, David PA, Mathis M, Unger E, Yang P, Khin NA. Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. J Clin Psychiatry 2014; 75(3):205-14.

2. Trivedi MH, Rush AJ, Gaynes BN, Stewart JW, Wisniewski SR, Warden D, Ritz L, Luther JF, Stegman D, Deveaugh-Geiss J, Howland R. Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR(*)D measurement-based care. Neuropsychopharmacology 2007; 32(12):2479-89.

SHOULD ANTIPSYCHOTIC MEDICATIONS FOR SCHIZOPHRENIA BE GIVEN FOR A LIFETIME?

Ira Glick, Stanford University School of Medicine

Individual Abstract: Background: Schizophrenia remains a major health problem despite antipsychotic medications that, for most patients, can decrease acute symptoms, decrease relapses, and contribute to partial and sometimes strong positive response in patients with chronic symptoms. What has not been clear—because a double-blind, randomized, placebo-controlled trial is not feasible or ethical—is how many years after the initial episode, or onset of antipsychotic treatment, should medication be continued to achieve the best global outcome. We designed a small, clinical study to retrospectively perform a detailed follow-up to examine antipsychotic medication because it relates to both global outcome and life satisfaction.
Methods: This is a naturalistic study of 35 patients with chronic schizophrenia examining antipsychotic medication adherence from 8 to 50 years (average, 21 y) after onset of antipsychotic treatment. The sample was derived from all patients treated for many years in 1 physician's academic clinic. Most were treated by community physicians before referral to the academic clinic. Information was gathered on (1) medication adherence, (2) long-term global outcomes (based on both the patient ratings and a blind clinician's assessment [blind to medication data] on both the Global Outcome Scale and the Global Assessment of Functioning Scale), and (3) a patient-rated Satisfaction With Life Scale. Spearman rank order correlations were used to relate medication adherence to global outcomes and life satisfaction, as were linear regression models adjusted for demographic and clinical characteristics.

Results: A total of 35 patients (mean age, 45 y; mean years of possible medication since onset of treatment, 21 y) were assessed. Medication adherence was a statistically significant predictor of better long-term global outcomes and life satisfaction, both in Spearman rank order correlations and in covariate-adjusted linear regressions (all P values
Conclusions: In this naturalistic study, patients who adhered to antipsychotic medication had better long-term global outcomes than those who had poor adherence. Study limitations include the potential for residual confounding. This sample provides data consistent with the recommendation, in the absence of clinically important unwanted drug effects like tardive dyskinesia or large weight gain, for continuous, long-term treatment for chronic schizophrenia.

Learning Objectives

1. Results of long term medication treatment of schizophrenia.
2. Guidelines for lifetime treatment of schizophrenia.

Literature References

1. Glick I.D., Davis, J.M., Zamora, D., et al. Should Antipsychotic Medications for Schizophrenia be Given for a Lifetime? A Naturalistic Long Term Follow Up Study. The Journal of Clinical Psychiatry. 2017 37:125-130.
2. Schatzberg A.F., DeBatista C. Manual of Clinical Psychopharmacology. 8th Edition, American Psychiatric Press. Arlington VA. 2015 p. 1-13.

TREATMENT OF RESISTANT DEPRESSION WITH KETAMINE: SIMILARITIES AND DIFFERENCES WITH ECT*

Amit Anand, Cleveland Clinic Lerner School of Medicine of Case Western University

Overall Abstract: ECT has been in use for nearly 75 years for severe Treatment Resistant Depression and is considered to be one of the most effective treatments. However, treatment with ECT is associated with a number of drawbacks including requirement of general anesthesia, memory impairment and social stigma. In light of this, new treatments for severe TRD are being sought by patients and in recent times ketamine has emerged as a possible alternative and is being offered by a number of centers. However, how ketamine is given for the treatment for TRD continues to be fine-tuned and studies comparing ECT and ketamine treatments have not been conducted. In this panel, presenters will discuss new studies which have examined and compared ECT and ketamine treatments from different perspectives. Dr. Sanjay Mathew will address the issue of the possible better convenience of ketamine treatment as it may be possible to give it less frequently than ECT for TRD. He will present results of a study which compared whether once weekly or twice weekly ketamine is more effective. Dr. James Murrough will address the issue of durability of response after treatment with ketamine and issue which has been important regarding ECT treatment too. He will present results of a study which investigated the efficacy of combination treatment with ketamine and lithium for TRD and blood and brain-based biomarkers associated with ketamine's rapid treatment effect. Dr. Gerard Sanacora will present meta-analyses results of anti-suicidal properties of ECT and ketamine. Dr. Roman Dale will present current experience and results from a clinical registry for ECT and ketamine treatment and temperamental predictors of response in real-life ketamine treatment of TRD. At the end, Dr. Anand will discuss the comparison between ECT and ketamine treatments from the patients point of view. The methodology and current update from the ongoing large multi-site scale real-world comparative effectiveness study between ECT and ketamine for Treatment Resistant Depression (ELEKT-D) study funded by the Patient

Centered Outcome Institute (PCORI) will be presented. The topic will be opened up for discussion with questions from the audience.

Learning Objectives

1. Current treatment of Treatment Resistant Depression.
2. Role of ketamine for Treatment Resistant Depression.

KETAMINE DOSE FREQUENCY AND SHORT-TERM OUTCOMES IN TREATMENT-RESISTANT DEPRESSION

Sanjay Mathew, Baylor College of Medicine

Individual Abstract: Introduction: Numerous clinics have begun offering repeated administrations of ketamine in order to sustain its transient antidepressant response. However, there is substantial variability in administration schedules and limited information as to what constitutes an optimized dose-frequency schedule. A recent randomized controlled trial found that twice-weekly and thrice-weekly administrations of intravenous (IV) ketamine similarly maintained antidepressant efficacy over 15 days. We compared outcomes of patients receiving IV ketamine on a twice-weekly versus once-weekly infusion schedule in a naturalistic outpatient setting.

Methods: Thirty-eight depressed adults (58% female; mean age=41.9,SD=14.1) received six infusions of intravenous ketamine (0.5 mg/kg over 40 minutes) on a twice-weekly (n=22) or once-weekly (n=16) basis depending on patient preference. The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) was used to assess depression severity at baseline and immediately prior to each infusion. Repeated measures General Linear Models tested effects of infusion schedule on QIDS-SR scores. Fisher Exact Test compared infusion schedules in terms of response rates (>50% reduction from baseline QIDS-SR score), remission (QIDS-SR $\leq$5), and sustained response/remission (meeting criteria at the final two consecutive ratings).

Results: Ketamine was associated with a significant reduction in QIDS-SR scores across infusions (baseline mean=18.8,SD=4.3; post-5th infusion mean score=9.0,SD=5.9, $F(3.32,122.88)=54.28$,$p<.0001$), with an overall response rate of 66%. There was overall significant improvement in depression after the first infusion, with additional incremental improvements after the second and third infusions, such that 80% of responders did so by this latter time point. There were no effects of infusion schedule on decrease in depression severity ($F(3.31,119.21)=0.62$,$p=.62$) and no differences in response, remission, or sustained response/remission rates (all p's >0.05). There were also no between-group differences in the median number of infusions received prior to initial response ($p=.65$).

Conclusion: In this retrospective exploratory analysis, once-weekly ketamine infusions were not significantly different than twice-weekly infusions in the overall magnitude of reduction in depressive symptoms or response durability. Depressive symptoms improved through at least the third infusion, indicating that multiple infusions provided the quickest benefit. In comparison, patients receiving once-weekly infusions achieved that benefit only after three weeks. Patient-related factors, including proximity to infusion center, financial resources, and illness severity, may be critical considerations in implementing infusion schedules.

Learning Objectives

1. To review the published data on repeated dose ketamine infusions in treatment-resistant depression.

2. To understand factors which might contribute to beneficial outcomes for patients receiving multiple infusions of ketamine.

Literature References

1. Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, Pinter C, Murrough JW, Sanacora G, Shelton RC, Kurian B, Winokur A, Fava M, Manji H, Drevets WC, Van Nueten L: A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. Am J Psychiatry 2016;173(8):816-26.
2. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV: Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013;74(4):250-6.

COMPARING AND CONTRASTING THE DATA ON THE RAPID ANTI-SUICIDAL EFFECTS OF KETAMINE AND ECT

Gerard Sanacora, Yale University

Individual Abstract: There is wide agreement that treatments capable of rapidly alleviating suicide ideation and behavior remain an unmet need. Recent studies and meta-analyses have highlighted the rapid onset of anti-suicidal action associated with the use of ketamine and esketamine in the treatment of patients with severe mood disorders. However, less attention has recently been given to investigations into ECT's ability to produce rapid onset anti-suicidal effects. In the spirit of the recently initiated PCORI sponsored ELEKT-D study "Electroconvulsive therapy (ECT) vs. ketamine in patients with treatment resistant depression (TRD)" an overview of the available data examining the anti-suicidal properties of both ECT and ketamine will be presented. As there are no studies directly comparing the efficacy of these treatments in reducing suicidal ideation or behavior, this presentation will provide a critical review of the existing data from several studies, comparing and contrasting the findings. The results of a recent one-stage meta-analytic study of individual participant data from10 identified placebo comparison intervention studies including 167 participants with baseline suicidal ideation will be discussed. The study found moderate to large ketamine effects (Cohen's d=0.48-0.85) on reduction of suicidal thinking in the days following treatment. The study also found a significantly greater proportion of ketamine treated patients became free from suicidal ideation compared with control treatments over the next week with a number needed to treat in the range of 3.1–4.0 for 1 to 7 days for being free of suicidal ideation after ketamine infusion. The results of this meta-analysis will be discussed along with other data from a recently reported proof of concept study specifically examining the rapid onset antidepressant and anti-suicidal effects of esketamine combination therapy in patients with major depressive disorder and imminent, active suicidal ideation or behavior. These data will be discussed alongside the evidence for ECTs rapid onset anti-suicidal effects. The American Psychiatric Association Professional guidelines specifically suggest ECT be considered for patients at high risk for suicide and in whom a particularly rapid antidepressant response is required. These recommendations are supported in part by findings from several studies over decades of time showing suicidal ideation to decrease rapidly after the initiation of ECT. However, this data comes largely from open-label and retrospective analyses, and there is relatively sparse data examining the more rapidly acting effects of ECT on suicidal ideation and behavior in controlled trials. The data from these reports will be critically reviewed and compared to the existing data with use of ketamine. The findings of the overall review highlight the need for more organized data collection methods related to rapid onset anti-

suicidal effects of both treatments and provides some insights into the relative values of the treatments in clinical settings.

Learning Objectives

1. To familiarize the attendees with the existing literature related to the rapid onset of anti-suicidal effects of ECT and ketamine.
2. To increase awareness on the need for more organized approaches to data collection related to the rapid onset of anti-suicidal effects on newly developed and existing treatments.

Literature References

1. Wilkinson ST, Ballard ED, Bloch MH, et al: The effect of a single dose of intrave nous ketamine on suicidal ideation: A systematic review and individual participant data meta-analysis. Am J Psychiatry 2017 [Epub ahead of print].
2. Fink M1, Kellner CH, McCall WV: The role of ECT in suicide prevention. J ECT. 2014 Mar;30(1):5-9.

PHARMACOLOGICAL STRATEGIES FOR TREATMENT RESISTANT DEPRESSION: AUGMENTATION OF KETAMINE THERAPY AND OTHER NOVEL APPROACHES

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Background: Treatment Resistant Depression (TRD) – affecting up to one third of all patients who suffer from major depressive disorder (MDD) – is associated with a chronic and disabling course of illness and a tremendous public health burden. Identifying new, more effective treatments for TRD is a major goal of biological psychiatry. Recently, the glutamate NMDA receptor antagonist ketamine has demonstrated rapid antidepressant effects in patients with TRD. The benefit of ketamine, however, is transient (e.g., up to one week following a treatment session), unless the ketamine treatment period is continued. The current talk will address this gap in knowledge and review results for recent clinical trials designed to test ways to continue or maintain the beneficial effects of ketamine in patients with depression.
Methods: Driven by the recent characterization of the molecular mechanisms underpinning the antidepressant and neuroplasticity effects of ketamine, we tested the combination of ketamine plus lithium in patients with TRD using a randomized, double blind, placebo-controlled design. Key to our hypothesis, both ketamine and lithium are potent inhibitors of glycogen synthase kinase (GSK)-3. In this study, N=47 patients with TRD were enrolled and underwent an initial (IV) infusion of ketamine (0.5 mg/kg). Of the 47 treated patients, N=35 met response criteria and were eligible for randomization. Of these, N=34 continued in the study and were exposed to at least one dose of lithium or placebo, and represent the intention to treat analyzed sample (ITT). The primary outcome was MADRS score two weeks following the last of 4 ketamine infusions.
Results: In this study, lithium did not show benefit over placebo in extending the antidepressant response to ketamine. The estimated coefficient for the indicator of lithium treatment was 0.051 (SD 3.89, p=0.99). Other strategies that will be considered in this talk include treatment with riluzole, SSRIs, repeated ketamine infusions, and oral ketamine. Maintenance ketamine infusions may be a viable alternative for some patients (data to be reviewed).
Conclusions: The addition of lithium does not appear to lead to reduction in depression compared to treatment with ketamine alone. Alternative strategies for augmenting and

maintaining the benefit of ketamine, however, show promise. Following the talk, the audience will understand the potential roles of ketamine and lithium in the treatment of TRD and be apprised of ongoing research aimed at extending the short-term benefit of ketamine.

Learning Objectives

1. To understand the role of ketamine and lithium in the treatment of treatment-resistant depression.
2. To be apprised of ongoing research aimed at extending the short-term benefit of ketamine, including the combination of ketamine with other medications designed to enhance neuroplasticity.

Literature References

1. Murrough JW, Abdallah CG, Mathew SJ: Targeting glutamate signalling in depression: progress and prospects. Nat Rev Drug Discov 2017; 16:472–486.
2. Murrough JW, Iosifescu DV, Chang LC, Jurdi RK Al, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ: Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013; 170:1134–1142.

TEMPERAMENT AS MODERATOR OF KETAMINE RESPONSE IN TREATMENT RESISTANT DEPRESSION – EXPERIENCE FROM A KETAMINE CLINICAL REGISTRY

Roman Dale, Cleveland Clinic

Individual Abstract: Background: Ketamine treatment is increasingly being given for treatment resistant depression (TRD) but it is unclear what kind of patients respond to it. It has been suggested that patient temperament characteristics may be related to response to medications. In this report we will describe our experience in running an ECT and ketamine treatment clinic registry for TRD patients. As part of a ketamine treatment registry, we assessed patient temperament profile and then related it to response to ketamine after initial two infusions.

Method: Patients with TRD who did not have a satisfactory response to antidepressant medications as well as ECT in the past were included for ketamine treatment. All patients completed the NEO-Five-Factor-inventory (NEO-FFI) which has 60 items and assesses with 12-item each temperament characteristics of – 1) Openness to experience; 2) Conscientiousness; 3) Extraversion; 4) Agreeableness; and 5) Neuroticism. Patients were treated with two infusions of ketamine 0.5mg/kg given over 40 minutes. Patients also completed the Montgomery Asberg Depression Rating Scale (MADRS) after each infusion. Response to treatment was defined as >50% decrease of MADRS score from pre-treatment visit to end of second ketamine infusion. An analysis of covariance was conducted to analyze differences between responders (RESP) and non-responders (NRESP), using age and gender as covariates, for the five subscales scores of the NEO-FFI.

Results: Data is available from 39 subjects (Age 49+14 yrs; 25F). Out of 39 subjects 19 subjects were RESP and 20 were non-responders NRESP. RESP group had a significantly higher scores on the Openness subscale of the NEO-FFI ($F = 6.6$, $P = 0.014$). Difference on the scores of the rest of the four subscales was not significant.

Conclusion: We identified the temperamental trait of Openness as related to ketamine response in TRD patients who had not responded to medication as well as ECT. These findings need to

be replicated in a larger controlled study. Temperamental characteristics may need to be kept in mind when considering ketamine treatment for patient with TRD. We will discuss these findings as well as our experience in running a clinical registry of treatment of TRD patients with ketamine and ECT.

Learning Objectives

1. Patient characteristics as moderators of treatment response with ketamine.
2. Lessons learned from a ketamine clinical registry.

Literature References

1. Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. J Affect Disord. 2013;147(1-3):416-20.
2. Szymkowicz SM, Finnegan N, Dale RM. Failed response to repeat intravenous ketamine infusions in geriatric patients with major depressive disorder. Journal of clinical psychopharmacology. 2014;34(2):285-6.

GERIATRIC PSYCHOPHARMACOLOGY UPDATE: FINDINGS, CHALLENGES, AND NEW OPPORTUNITIES*

George Niederehe, National Institute of Mental Health

Overall Abstract: Older adults are often underrepresented in clinical trials research. Given the advancing age of the population and the polypharmacy often seen in the elderly, more work needs to be done examining both efficacy and effectiveness of psychotropic medications in older adults. In addition, new advances in clinical neuroscience have pushed for the identification of biomarkers and correlates of treatment response variability. The National Institute of Mental Health (NIMH) has supported both large scale efficacy studies, as well as mechanism focused clinical examinations of both safety and tolerability among older adults. This symposium will highlight findings from NIMH supported trials in geriatric populations examining these themes. Topics will include: 1) Safety and efficacy of antipsychotic augmentation in older adults with psychotic depression 2) Effective treatment of Geriatric Mania; and 3) A preliminary experimental medicine trial of Buprenorphine for treatment resistant late life depression. Experts in the fields of clinical pharmacotherapy in late-life neuropsychiatric disorders will highlight the role of translational research and the use of these techniques for the development and advancement of clinical practice.

Learning Objectives

1. Discuss safety and side effect profiles from the STOP-PD trial.
2. Discuss clinical efficacy and safety findings from the GERI-BD study.
3. Discuss the role of neuroimaging and target engagement for the development of new therapeutic approaches.

SUSTAINING REMISSION OF PSYCHOTIC DEPRESSION: THE STOP-PD II STUDY -- FOCUS ON OLDER ADULTS

Ellen Whyte, University of Pittsburgh School of Medicine

Individual Abstract: Acute episodes of Psychotic depression (PD) are associated with

severe morbidity and disability, especially among older individuals. Treatment guidelines recommend either electroconvulsive therapy or the combination of an antidepressant drug and antipsychotic drug for the acute treatment of PD. Unfortunately, relapse and recurrence are common. Little is known about continuation pharmacologic treatment in PD, specifically whether an antipsychotic medication needs to be continued once an episode of PD responds to combination pharmacotherapy. This issue is of great clinical importance -- premature discontinuation of antipsychotic medication has the potential risk of early relapse of a severe and potentially lethal disorder whereas the unnecessary continuation of antipsychotic medication can expose a patient to adverse effects, such as weight gain and metabolic disturbance.

This session will present the results of a NIMH-funded, multicenter randomized placebo-controlled trial (STOP-PD II) that assessed the risks and benefits of continuing antipsychotic medication in younger and older adults with PD once the episode of depression has responded to combined treatment with an antidepressant (sertraline) and an antipsychotic (olanzapine). Of the 269 participants with an acute episode of PD who consented to acute treatment phase, through which they received combined treatment, 126 experienced remission and consented to the relapse prevention phase during which they were randomized to sertraline + olanzapine or to sertraline + placebo. Of these, 42.9% (n=54) were aged 60 or older. The final study participant completed the study in July 2017; analysis is ongoing.

In this presentation, we will (1) discuss the rationale for STOP-D II study and describe the aims and hypotheses, design, and methods of study; (2) present the main risk-benefit outcome of this study, namely the risk of continuation vs. discontinuation of the antipsychotic in the continuation phase with respect to relapse of the illness and risk of weight gain and metabolic dysfunction; and (3) contrast the main outcome between older vs. younger participants.

Learning Objectives

1. Understand the rationale, design, and methodology of STOP-PD II.
2. Understand the unique risks and benefits of continuing antipsychotic medication in older persons with remitted psychotic depression.

Literature References

1. Flint AJ, Rothschild AJ, Whyte EM, Mulsant BH, Meyers BS, for the STOP-PD II Study Group. Sustaining remission of psychotic depression: Rationale, design and methodology of STOP-PD II. BMC Psychiatry, 2013, 13:38-49.
2. Meyers BS, Flint AJ, Rothschild AJ, Mulsant BH, Whyte E, Peasley-Miklus C, Heo M, Papademetriou E, Leon A, for the STOP-PD Study Group: A double- blind randomized controlled trial of olanzapine plus sertraline versus olanzapine plus placebo for psychotic depression - the STOP-PD study. Arch Gen Psychiatry 2009, 66:838–847.

BUPRENORPHINE FOR MID- AND LATE-LIFE TREATMENT RESISTANT DEPRESSION: MECHANISMS OF ACTION AND CLINICAL EFFECT

Jordan Karp, University of Pittsburgh

Individual Abstract: Buprenorphine is being studied for treatment-resistant depression because of its kappa opioid antagonism; however, it is a complex molecule with multiple active metabolites and activity at multiple opioid receptors. We examined limbic and reward circuit changes during a trial of buprenorphine augmentation.

31 older adults with major depression incompletely responsive to an adequate trial with venlafaxine XR were randomized to augmentation with low-dose buprenorphine or matching placebo. We investigated neural changes using functional magnetic resonance imaging (fMRI) from pre-randomization to 3 weeks during both an emotional reactivity task and a gambling task, and their association with depressive symptom changes over 8 weeks and with concentrations of buprenorphine and its active metabolites at week 3.
Participants in both groups showed similar changes in depressive symptoms. In both groups, increases in rostral anterior cingulate (rACC) and ventromedial prefrontal cotex (vmPFC) activation during the emotional reactivity tasks were associated with overall symptom improvement. In the buprenorphine but not the placebo group, increased activation in left anterior insula (aINS) and bilateral middle frontal gyrus (MFG) was associated with improvement on the dysphoria subscale. Brain activation changes in the reward task did not differ for either group.
While we did not observe clinical superiority of low-dose buprenorphine in this pilot study, this is the first study to show differential neural changes during an emotion reactivity task with buprenorphine for depression treatment. Buprenorphine and placebo alter rACC/vmPFC activation, while only buprenorphine alters aINS/MFG activation. Lack of a difference between the groups during the reward task may support the relative safety of low-dose buprenorphine for not precipitating addictive behavior in carefully selected patients.
This experimental medicine project opens a window into how the aging depressed brain changes during exposure to low-dose BPN and provides pilot data on its clinical effect.

Learning Objectives

1. Appreciate how the opioid system is dysregulated in depression and understand the evidence for how modulation of this system may provide a novel intervention for treatment resistant depression.
2. Describe differences in neural changes during an emotion reactivity task in depressed midlife and older adults during treatment with low dose-buprenorphine or placebo.

Literature References

1. Karp JF, Butters MA, Begley A, Miller MD, Lenze EJ, Blumberberger D, Mulsant B, Reynolds CF. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. Journal of Clinical Psychiatry 2014;75(8):e785-93.

2. Fava M, Memisoglu A, Thase ME, et al. Opioid Modulation With Buprenorphine/Samidorphan as Adjunctive Treatment for Inadequate Response to Antidepressants: A Randomized Double-Blind Placebo-Controlled Trial. American Journal of Psychiatry 2016;173(5):499-486.

LITHIUM AND DIVALPROEX IN THE TREATMENT OF OLDER PATIENTS WITH BIPOLAR MANIA: GERI-BD

Robert Young, Weill Cornell Medical College

Individual Abstract: Objectives/Content: Despite an increasing number of elders with bipolar disorder (BD), evidence to guide treatment of late-life mania has been lacking. We compared the tolerability and efficacy of lithium carbonate (LI) and divalproex sodium (DVP) in older

adults with bipolar mania. We hypothesized that DVP would be better tolerated and more efficacious than LI.
Methods: We conducted a randomized, double-blind acute treatment study at academic psychiatric services. The participants were aged > 60 years, had BD type I, and presented with a manic, hypomanic or mixed episode. They were randomized to LI (target serum concentrations: 0·80-0·99 mEq/L) or DVP (target: 80-99 mcg/ml) for 9 weeks. Participants with inadequate response after 3 weeks received open adjunctive risperidone. Tolerability was assessed based on a measure of sedation and on the proportion achieving target concentrations. Efficacy was assessed with the Young Mania Rating Scale (YMRS).
Results: Among the randomized participants (n= 224) attrition rates were similar for LI and DVP. The groups did not differ in ratings of sedation. A similar proportion of participants achieved target concentrations. A longitudinal mixed-model of symptomatic improvement (YMRS change from baseline) statistically favored LI at week 9. However, differences in response rates were not statistically significant. The need for adjunctive risperidone was low and was similar for LI and DVP.
Discussion: Clinicians and investigators should bear in mind the role of classical mood stabilizers in the management of older patients with BD.

Learning Objectives

1. Findings from an NIH-funded randomized, double-blind controlled trial comparing lithium and divalproex in older adults with bipolar manic states.
2. The limited existing evidence regarding mood stabilizer treatment of bipolar disorder in old age, and the implications of these findings for practice and further research.

Literature References

1. Forester B, Gildengers AG, Young RC: Biological factors in bipolar disorders in late life. In: Bipolar disorder. Basic mechanisms and therapeutic implications. Edited by J Soares, A Young, 3rd ed. Cambridge U. Press, New York, 2016, pp 234-249.
2. Young RC , Mulsant BH, Sajatovic M, Gildengers A, Gyulai L, Al Jurdi RK, Beyer J, Evans J, Banerjee S, Greenberg R, Marino P, Kunik ME, Chen P, Barrett M, Schulberg HC, Bruce ML, Reynolds, CF, Alexopoulos GS: GERI-BD: A randomized, double-blind, controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. Am.J. Psychiatry 174 (11): 1086- 1093.

Workshop Sessions
2:45 p.m. - 4:45 p.m.

AN AFSP/ASCP WORKSHOP: INCLUSION OF SUICIDAL INDIVIDUALS IN TREATMENT TRIALS: NOW IS THE TIME
Jill Harkavy-Friedman, American Foundation for Suicide Prevention

Overall Abstract: For many years and for a variety of reasons investigators conducting clinical trials have excluded individuals from participating in studies when they report suicidal ideation or past attempts. Since suicidal individuals represent a large proportion of individuals with mental health conditions, up to 30-50% for some diagnostic groups, real world trials must figure out how to include suicidal. Dr. Canuso, the first speaker, will discuss the S-Ketamine trial which focuses on treating the person with suicidal ideation. Dr. Canuso will discuss how

to facilitate the process of recruiting and studying individuals with suicidal ideation and behavior including gains from the process as well as how to approach adverse events. Dr. Sullivan will then discuss the treatment of insomnia, a symptom frequently present for suicidal individuals and how to incorporate assessments into the process of a clinical trial. Representing NIMH, Dr. Avenevoli, will discuss how the current climate is poised to address the problem of suicide. The workshop will include a discussion of including suicidal individuals in clinical trials from a regulatory perspective from Dr. Farchione of the FDA and Dr. Pani of EMA. The workshop will conclude with an interactive dialogue about how to implement this important shift in clinical trials.

Learning Objectives

1. Understand in the importance of including a suicidal person in a clinical trial.
2. Understand the importance of targeting suicidal ideation or behavior for treatment.

INCLUSION OF SUICIDAL INDIVIDUALS IN TREATMENT TRIALS: INSIGHTS FROM AN ONGOING PHASE 3 DRUG DEVELOPMENT PROGRAM

Carla Canuso, Janssen Research & Development

Individual Abstract: Since the FDA issued draft safety guidance in 2010, pharmaceutical companies developing drugs for psychiatric and certain neurological indications have been required to prospectively assess suicidal ideation and behavior (SI/B), and utilize the Columbia Classification Algorithm for Suicide Assessment (C-CASA) to code these data in clinical trials. In parallel with the need to systematically characterize the SI/SB-related safety of CNS drugs, interest in developing treatments for SI/SB has grown. In 2015 a Consensus Meeting on Methodological Considerations for Suicide Assessment and Clinical Trial Design was convened with the aims to review what has been learned about the implementation of SI/SB assessments in industry-sponsored clinical trials, to work towards a consensus on the standardization of SI/SB data collection and analysis, and to develop recommendations to guide the development of novel treatments for SI/SB.1

Today 3 pharmaceutical companies are developing treatments targeting the rapid reduction of suicidal ideation in depression (2 in Major Depressive Disorder and 1 in Bipolar Depression), utilizing several agents from the new class of potentially rapidly acting antidepressants. These novel agents, as well as an under-studied and vulnerable patient population, present new clinical, methodological and regulatory considerations.

Based on experience from a recently conducted Phase 2 trial2 and an on-going global Phase 3 program of esketamine for the rapid reduction in symptoms of MDD, including suicidal ideation, this presentation will outline some of the key considerations and challenges in designing and implementing a drug development program for patients at imminent risk for suicide. These topics will include target indication, subject selection, efficacy outcomes, safety management and monitoring, comparators, signal-detection, operational challenges, regional differences and ethical considerations. Preliminary data on subjects' clinical and demographic features at baseline will also be presented. Additionally, alternative approaches employed in other ongoing development programs targeting acutely suicidal patients will be discussed.

This presentation will demonstrate that, from an Industry Perspective, including suicidal patients in clinical trials is indeed feasible and can be implemented safely. Moreover, the presentation will share methodological insights for the development of much needed treatments for patients at imminent risk for suicide.

Learning Objectives

1. Attendees will gain insight into the Industry Perspective on the inclusion of suicidal patients in clinical trials.
2. Attendees will understand some of the considerations and challenges in designing and implementing a drug development program for patients at imminent risk for suicide.

Literature References

1. Chappell, P. et al., Assessment of Suicidal Ideation and Behavior: Report of the International Society for CNS Clinical Trials and Methodology Consensus Meeting. J Clinical Psychiatry, 2017.
2. Canuso, C.M. et al., Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry, In Press.

INCLUDING SUICIDAL INDIVIDUALS IN MULTICENTER TREATMENT TRIALS: TREATMENT OF MILITARY-RELATED PTSD WITH TNX-102 SL*, A NOVEL FORMULATION OF CYCLOBENZAPRINE HYPOTHESIZED TO ADDRESS PTSD THROUGH IMPROVEMENT IN SLEEP QUALITY

Gregory Sullivan, Tonix Pharmaceuticals, Inc.

Individual Abstract: Background: It has been common in clinical trials to exclude individuals who express suicidal ideation (SI) or have a history of attempt. Yet, when studying a psychiatric conditions with elevated SI and attempts such as posttraumatic stress disorder (PTSD), this approach will result in a substantial portion never being studied for the safety and efficacy of the intervention. Also, critical research data from a sample enriched for SI and suicidal behaviors (SB) are lost. To demonstrate the feasibility of including participants with SI and/or past suicide attempts, Dr. Sullivan will discuss both the rationale for inclusion of such participants, and the suicidality data that emerged, in a Phase 2 multicenter trial of TNX-102 SL in military-related PTSD, the 'AtEase' study. Sleep disturbances, mood disorders, and PTSD in the military have all been associated with elevated rates of SI and SB, and those with military PTSD typically express this full constellation of risk factors. The specific suicidality inclusions and exclusions for the AtEase protocol, the suicidality assessments employed (C-SSRS, MINI Suicidality module B, MADRS item 10, also CAPS-5 item 16[E2]), and the approaches to addressing safety will each be reviewed.

Methodology: The AtEase study was a Phase 2, randomized, double-blind, placebo-controlled, multi-center safety and efficacy study of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) in military-related PTSD. Twenty-four clinical trial sites across the US randomized 245 participants into three treatment arms for nightly bedtime dosing for 12 weeks: placebo, TNX-102 SL 2.8 mg, and TNX-102 SL 5.6 mg. Eligible participants were male or female, between 18-65 years old, and had experienced DSM-5 PTSD criterion A-qualifying trauma(s) during military service since 2001. All met PTSD diagnosis by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) "Past Month Version," and were not currently using antidepressants and other excluded psychotropics at randomization, or receiving any form of trauma-focused psychotherapy. The specific SI and SB inclusions/exclusions were based on: 1) the Columbia-Suicide Severity Rating Scale (C-SSRS) and 2) the Mini International Neuropsychiatric Interview, 7.0 (MINI) Suicidality module. Also administered were the Montgomery-Åsberg Depression Rating Scale, with item 10 on SI; and the CAPS-5 item 16[E2] reckless or self-destructive behavior, which includes SB. The protocol recommended

that a Safety Planning Intervention (SPI) or similarly intensive intervention for safety be implemented in all participants with C-SSRS types 2 and/or 3 SI.
Results: At screening, lifetime prevalence of SI, suicide plans, and actual attempts were 32.1%, 8%, and 5.5%, respectively, higher rates than reported by Nock et al (2014) among US Army soldiers in a cross-sectional survey of 5428 nondeployed soldiers. A more granular look at the prevalence of SI and SB in the AtEase participants, and the changes over the course of the trial by treatment arm will be presented. The approach to adverse events involving SI and SB will also be discussed.
Conclusions: With the SPI added to the study, these data support the feasibility of greater inclusion of suicidal individuals in CNS trials for better representation of the populations with specific disorders such as PTSD. Moreover, since suicides and suicide attempts are relatively rare events in clinical trials, studies such as this contribute to the cumulative data across investigational drug trials (in the same or different indications), providing a valuable source for meta-analyses to elucidate the predictive risk factors for SB and the responses of these behaviors to pharmacological treatments.

Learning Objectives

1. Describe typical rates of suicidal ideation and behaviors found in populations with military-related PTSD.
2. Analyze the implementation of inclusion of individuals with suicidal ideation and behaviors in a large, multicenter clinical treatment trial.

Literature References

1. Nock MK, Stein MB, Heeringa SG, et al: Prevalence and correlates of suicidal behavior among soldiers – results from the Army study to assess risk and resilience in servicemembers (Army STARRS). JAMA Psychiatry 2014; 71:514-522.
2. Armoura C, Fried EI, Deserno MK, Tsai J, Pietrzak RH: A network analysis of DSM-5 posttraumatic stress disorder symptoms and correlates in U.S. military veterans. Journal of Anxiety Disorders 2017; 45:49–59.

THE NIMH PERSPECTIVE ON SUICIDE PREVENTION RESEARCH

Shelli Avenevoli, National Institute of Mental Health/NIH

Individual Abstract: The NIMH mission is to transform the understanding and treatment of mental illness through basic and clinical research, paving the way for prevention, recovery and cure. Preventing suicide is a research priority at NIMH, and we have partnered with the National Action Alliance for Suicide Prevention (NAASP) and the American Foundation for Suicide Prevention to reduce suicide rates 20% by 2025. This presentation will provide an overview of NIMH research priorities, initiatives, partnerships, and scientific advances related to the prevention of suicide, with an emphasis on emerging research directions and areas ripe for implementation. With regard to the inclusion of suicidal individuals in clinical trials, the NAASP Prioritized Research Agenda for Suicide Prevention recommended this pathway to progress: "Expand pharmaceutical industry trials so that new and repurposed medication trials target suicidal symptoms and related cognitive dysfunction (e.g., anhedonia, hopelessness, impulsivity) in order to increase the number of available pharmacological treatment options that might mitigate suicidal risk. Consider policies to encourage safe and fair recruitment of suicidal patients in trials, including consistent approaches to assessing adverse events. (p.31)." In accordance with this recommendation, the presentation will offer the NIMH perspective on

the inclusion of suicidal individuals in clinical trials, examples of NIMH-funded efforts, and the role of funders in supporting these approaches.

Learning Objectives

1. Garner knowledgeable about NIMH priorities for suicide prevention.
2. Learn about NIMH funded studies on suicide prevention.

EARLY CAREER WORKSHOP: HOW TO GET PUBLISHED

Ross Baker, Otsuka

Overall Abstract: Mirjana Domakonda, Hartford Hospital/Institute of Living will begin by discussing 10 Helpful Tips on how to get published. Ross Baker, Otsuka, will follow an overall discussion on authorship and industry papers, including how to get involved. Presenters will provide a combination of discussion and didactic sessions, starting with Leslie Citrome, Editor, International Journal of Clinical Practice, that will discuss what journal editors look for in a paper. Marlene Freeman, Editor, The Journal of Clinical Psychiatry and Erika Saunders, Editor of the Early Career Psychiatry section of The Journal of Clinical Psychiatry, will discuss where to submit papers. Cameron Carter, Editor, Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, will discuss how to respond to reviewer comments. Roy Chengappa, Editor, Bipolar Disorders, will discuss editor expectations for peer reviewers.

Learning Objectives

1. To understand the processes involved in how a manuscript gets evaluated.
2. To begin to assess the "lay of the land" in terms of journal selection.
3. The participants should be able to understand the role of a peer reviewer in the peer review process of a paper that is submitted to a journal.

WHAT DO JOURNAL EDITORS LOOK FOR?

Leslie Citrome, Editor*, International Journal of Clinical Practice*

Individual Abstract: The massive influx of manuscripts being submitted to medical journals make it important to make sure your paper stands out. Not all manuscripts get sent out for external peer review and thus the first hurdle is to ensure alignment between your paper and the target journal. To be discussed are: journal selection, the importance of a pre-submission inquiry, reasons why papers get accepted, and reasons why they are rejected.

Learning Objectives

1. To understand the processes involved in how a manuscript gets evaluated.
2. To understand how to maximize the chances of success in having your paper published.

Literature References

1. Citrome L. How do I get my manuscript accepted? Steps and missteps. Int J Clin Pract. 2016 Feb;70(2):97-8.
2. Chipperfield L, Citrome L, Clark J, et al. Authors' Submission Toolkit: a practical guide to getting your research published. Curr Med Res Opin. 2010 Aug;26(8):1967-82.

WHERE TO SUBMIT YOUR PAPERS

Marlene Freeman, Editor, *The Journal of Clinical Psychiatry and Erika Saunders,* Editor of the Early Career Psychiatry section of *The Journal of Clinical Psychiatry*

Individual Abstract: Publishing your work is an essential part of an academic career, and a crucial aspect of building your CV regardless of your ultimate career goals. In this workshop, one focus will be upon how to select a journal to which you will submit your work. We will discuss an overview of the submission process, from journal selection to publication. The inner workings of the process will be revealed! This will be a highly interactive session, and questions will be welcome.

Learning Objectives

1. To begin to assess the "lay of the land" in terms of journal selection.
2. To increase understanding of the Journal process, from submission to publication.

Literature References

1. Saunders EF. Early career psychiatrists. Introduction. J Clin Psychiatry. 2015 Oct;76(10):1373.
2. Freeman MP. J Clin Psychiatry. 2013 Nov;74(11):1092.

THE PEER REVIEW PROCESS AND JOURNAL EDITORS EXPECTATIONS FOR PEER REVIEWERS

Roy Chengappa, Editor, *Bipolar Disorders*

Individual Abstract: The Peer Review process is of primary importance to peer reviewed journals! It could be argued that the fate of submitted manuscripts selected to be sent out for peer review depend to a large extent on the assessment of the peers who review them and the recommendations they make to the editors and the authors. This short presentation and discussion will review the expectations that editors and editorial office staff have of peer reviewers including their roles and responsibilities. These responsibilities include but are not limited to letting the editors know of any conflicts of interest, the inability to review in a timely manner or wanting to review but requiring more time, providing sufficient time for assessment of the paper and writing a thoughtful and trustworthy review, keeping materials confidential, not using the materials for their own or others' advantage, among others. Objectivity and constructive criticism are givens but not always achieved, and defamatory or personal insults are obviously unacceptable. It is advisable for reviewers to provide the editors with information if this article was previously reviewed by them, and whether any of the changes they had requested have been made in this submission. Instances of outright plagiarism or other unethical issues (e.g. duplicate publication, fabrication, or others) relating to the submission should be brought to the attention of the editors. The peer review is still mainly a "honor system", i.e. done as "part of the job" by the community of researchers in a particular field, and also in the majority of cases, without compensation. The main model of journal peer review remains the "blinded" peer review in which the reviewers know who the authors are but the authors do not know who the reviewers are, there are rare models that accommodate "double-blind" reviews where both the reviewers and authors are "blinded" but as can be expected this level of blinding is hard to achieve. There is also the "open" review journal model where the reviewers and authors can see online who is reviewing and commenting on the submission.
Journal editors and editorial office staff and publishers recognize the precious resource that a pool of excellent peer reviewers constitutes and we salute them for their work. The assessment and review by peer reviewers, and recommendations they make for revisions, minor or major,

or rejection or acceptance typically form the basis by which editors and editorial boards decide which papers make it into the journal or not. Reviewers can take opposite positions on a submission, and editors and editorial board members may have to arbitrate on the eventual outcome of the submission.

Learning Objectives

1. The participants should be able to understand the role of a peer reviewer in the peer review process of a paper that is submitted to a journal.
2. The participants should be able to review and understand the expectations that journal editors, editorial board members, or editorial staff have of peer reviewers in the processing and outcomes of papers submitted to a peer reviewed journal.

Literature References

1. Irene Hames, 2007. Peer Review and Manuscript Management in Scientific Journals. Guidelines for Good Practice. Blackwell Publishing, Oxford UK and Malden, USA. Published in association with the Association of Learned and Professional Society Publishers (www.alpsp.org).
2. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder (pages 97–170).
3. Lakshmi N Yatham, Sidney H Kennedy, Sagar V Parikh, Ayal Schaffer, David J Bond, Benicio N Frey, Verinder Sharma, Benjamin I Goldstein, Soham Rej, Serge Beaulieu, Martin Alda, Glenda MacQueen, Roumen V Milev, Arun Ravindran, Claire O'Donovan, Diane McIntosh, Raymond W Lam, Gustavo Vazquez, Flavio Kapczinski, Roger S McIntyre, Jan Kozicky, Shigenobu Kanba, Beny Lafer, Trisha Suppes, Joseph R Calabrese, Eduard Vieta, Gin Malhi, Robert M Post and Michael Berk Version of Record online: 14 MAR 2018 | DOI: 10.1111/bdi.12609.

30 YEARS OF THE PANSS IN SCHIZOPHRENIA: WHERE ARE WE NOW AND WHERE ARE WE HEADED?

Jean-Pierre Lindenmayer, New York University

Overall Abstract: Thirty years ago, Stanley Kay and colleagues developed the Positive and Negative Syndrome Scale (PANSS) to assess the presence and severity of psychopathology symptoms in schizophrenia, primarily to measure the efficacy in antipsychotic drug trials. For the past 30 years, the PANSS has been administered in thousands of international clinical trials to an estimated 3 million individuals and approved by the Food and Drug Administration (FDA) as a primary endpoint. Since then, the PANSS has been used to measure overall levels of psychopathology in studies of schizophrenia covering cognitive, imaging, genetic, pathophysiological and non-pharmacological treatment response studies. Several pertinent changes have been utilized, such as the use of the factor scores for symptom constructs, shortened versions of the PANSS based on Item Response Modeling, linking the PANSS to global severity scales, dichotomizing the construct of negative symptoms and interpretations of meaningful change. Additionally, changes in the clinical research landscape have occurred, for example, the Research Domains Criteria (RDoC) initiative aimed to overcome limitations in the enduring diagnostic classification by exploring ways of classifying mental disorders constructed from "dimensions of observable behavior and neurobiological measures." How well does the PANSS perform with these new challenges and recommendations?

Jean Pierre Lindenmayer, MD will address historical perspectives on the PANSS and its widespread use as a primary efficacy endpoint in clinical trials. This will also encompass empirical data on the development of the PANSS, its use in clinical trials, different factor structures, item response models and considerations of shortened versions of the PANSS.
Larry Alphs, MD will explore how the PANSS measures negative symptoms and present an overview of other negative symptoms scales and their comparison with the PANSS and examine which negative symptom dimensions are captured and not captured by the PANSS.
David Wallings, PhD will present cross-cultural and linguistic comparisons of the PANSS across different languages. What do psychometric properties of the PANSS assessments across cultures show, and how are language and identity processes interpreted and scored across cultures?
Anzalee Khan, PhD will examine how new technologies and electronic devices have changed the way the PANSS is administered and scored. This will also address the use of links, algorithms, risk-based and real-time monitoring of PANSS data captured in clinical trials. As such, are modern statistical approaches able to refine the PANSS to produce a more reliable and psychometrically sound measurement of treatment efficacy?
Mark Opler, PhD will interrogate the future state of the PANSS and address questions whether the PANSS as it is being used at present replaceable by other assessment modalities, should advances in the disease area also yield to advances in measurement? What do the next 30 years hold for the PANSS and clinical assessments of schizophrenia? Should there be PANSS modules, which are illness-phase or age specific? How will the PANSS fare in the new RDoC framework and what are the next steps both psychometrically and clinically for the PANSS development?
The workshop presenters will open the discussion with the audience.

Learning Objectives

1. After this workshop the audience will have a better understanding of the psychometric changes the PANSS has undergone and how a shorter PANSS can be developed.
2. After this workshop the audience will have a better understanding of possible modifications of the PANSS to measure psychopathology in different illness phases and life span periods.

OVERVIEW OF NEGATIVE SYMPTOMS AND COMPARISON OF PSYCHOMETRIC PROPERTIES OF THE PANSS AND VARIOUS ALTERNATIVE NEGATIVE SYMPTOM INSTRUMENTS

Larry Alphs, Janssen Scientific Affairs, LLC

Individual Abstract: When Stanley Kay and colleagues developed the Positive and Negative Syndrome Scale (PANSS) they consciously sought to improve upon existing scales for measuring symptoms of schizophrenia and their response to treatment by including concepts of the disease that were then gaining broader recognition. As their titling suggests, the authors specifically sought to assess the presence and severity of negative symptoms in schizophrenia, so that their response to treatment could be more readily identified.
Since the development of the PANSS alternative instruments for the assessment of negative symptoms have come into use. These include the Schedule for the Assessment of Negative Symptoms (SANS), the Negative Symptom Assessment (NSA-16 and NSA-4), and the Schedule for Deficit Syndrome (SDS). In addition, two newer instruments are in development—the Clinical Assessment Interview for Negative Symptoms (CAINS) and the

Brief Negative Symptoms Scale (BNSS). The development of these multiple approaches has the potential to more deeply understand the construct of negative symptoms in relationship to that provided by the PANSS negative symptom subscale.
Assessments of negative symptoms are useful when addressing a variety of needs. The multiplicity of scales, presents challenges for understanding when best to use the different approaches. Among these are uses as 1) a screener for presence and severity of negative symptoms, 2) an assessment for response to treatment in a research or clinical setting and 3) measurement of effects on functioning. At a more fundamental level they might be used to address the validity and homogeneity of the negative symptom construct. To facilitate appropriate scale selection, researchers must consider the psychometric structure of potential scales, their coverage of identified symptom domains, the reliability and validity of information collected related to those domains and their sensitivity to change. Other considerations for scale selection relate to how information is collected. This includes who provides the information collected on the instrument: the patient, an external rater following a patient interview or other informants. Other psychometric questions like their integration of global scores should also be considered.
This presentation will address these key issues and how they relate to the information summarized by the negative symptom domain of the PANSS.

Learning Objectives

1. Participants in this session will gain a deeper knowledge of the psychometric characteristics of alternative scales that assess negative symptoms of schizophrenia.
2. Participants in this session will gain a better sense of how to choose among the various alternative scales for the assessment of negative symptoms.

Literature References

1. Axelrod BN, Goldman RS and Alphs LD. Validation of the 16-Item Negative Symptom Assessment J of Psychiatry Res 1993 Jul-Sep; 27(3):253-258.
2. Kane, J. Tools to assess negative symptoms in schizophrenia, J Clin Psychiatry 2013 Jun;74(6):e12. doi: 10.4088/JCP.12045tx2c.

A 30-YEAR VOYAGE: CROSS-CULTURAL IMPLICATIONS IN THE USE OF THE PANSS

David Walling, CNS Network, LLC

Individual Abstract: The Positive and Negative Syndrome Scale (PANSS) has long been considered the gold standard for the assessment of psychotic symptoms in clinical trials. As we celebrate 30 years of the instrument, it is important to examine its use as it pertains to cross-cultural research. The PANSS was developed in the US with English as the original language. There are now over 40 certified translations (and other versions that have not been certified) and regulatory authorities throughout the world have accepted its use. However, the translation of an instrument to various languages does not mean that the interpretation of the items is equivalent across cultures. Data from multiple large international trials have shown that there are regional differences in the use and interpretation of items on the PANSS, which can impact overall scoring. While many believe that the negative symptoms are the most difficult to rate across cultures, there are also regional differences that impact positive symptoms as well. What is not known is whether these variances are due to cultural factors or translational issues. Regional factors and cultural issues can also have implications for training raters in various

countries and for interpreting data. This presentation will focus on what is known about regional variables as well as implications for the use of the PANSS across cultures. The literature on regional differences in the PANSS will be reviewed and data will be presented from the presenter's own personal experience training on the PANSS in multiple countries.

Learning Objectives

1. Understand how the PANSS is used in international studies.
2. Understand regional differences in the use and scoring of the PANSS.

Literature References

1. Kay SR, Fizbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 1987; 13(2): 261-276.
2. Aggarwal NK, Tao H, Xu K, et al: Comparing the PANSS in Chinese and American inpatients: cross-cultural psychiatric analyses of instrument translation and implementation. Schizophrenia Research 2011; 132(2-3): 146-52.

TECHNOLOGICAL INNOVATIONS IN THE PANSS: HARNESSING THE DIGITAL REVOLUTION

Anzalee Khan, ProPhase LLC

Individual Abstract: Purpose: Digital technology has the capability to transform the way clinical rating scales are administered by capturing both patient and clinician reported outcomes digitally. There is increased evidence for obtaining improved data quality with digital systems over paper versions by using electronic clinical outcomes assessment (eCOA) in healthcare. Since eCOA can capture data on smartphones, tablets, browsers, interactive voice response systems, and patient's own devices (BYOD), using secure systems that meet regulatory guidelines for electronic data capture are becoming more protuberant. Digital online and mobile applications can offer raters and patients greater access to information and services and enhance clinical management and early intervention through access to real-time patient data. There are many existing eCOA adaptations of the PANSS that are in use in clinical trials.
Content: Programming a PANSS into a digital system may assist with reducing errors by eluding errors in logic (e.g., scoring), but the technology alone cannot address the variability in clinicians understanding of symptoms and anchors in the PANSS. As operation and the use of an electronic PANSS grows, additional information is needed to provide a more complete understanding of how to use it effectually to obtain the benefit of improved data quality.
Methodology and Results: Data will be presented from electronic PANSS scales in use in clinical trials with a focus on: can the use of an electronic PANSS can represent an integrated eCOA system to promote increased patient reporting of events, real-time data for review, built-in algorithms for discrepancy checks, clinician feedback, on-device training tools for clinicians, and training on patient engagement, to deliver maximum benefits from the use of technology. The workshop will address how assembling high quality data for clinical trials and clinical services requires an integrated clinical science and technology system.
Importance: It is recognized that considerable gaps exist in the evidence base underlying new technologies. Additional involvement from patient, clinician, scientist, and regulatory bodies is needed to evaluate digital technologies and ensure they target unmet needs of clinical trials, maintain regulatory standards and improve clinical outcomes.

Learning Objectives

1. The audience will be able to understand how electronic versions of the PANSS are being administered in clinical trials, and how combining science and technology can enable better interview experience with the PANSS.
2. The audience will receive and overview of the benefits of quality data collection, and whether strategies such as training and patient engagement can be achieved through electronic adaptations of the PANSS.

Literature References

1. Khan, A et al. 2013. Assessing the sources of unreliability (rater, subject, time-point) in a failed clinical trial using items of the Positive and Negative Syndrome Scale (PANSS). Journal of Clinical Psychopharmacology.33(1):109-17.
2. Kobak KA; Feiger,AD; Lipsistz, JD. 2005 .Interview Quality and Signal Detection in Clinical Trials." American Journal of Psychiatry, 162(3), p. 628.

THE PANSS: PRESENT STATE AND FUTURE DEVELOPMENTS

Jean-Pierre Lindenmayer, New York University

Individual Abstract: Over the past 30 years the PANSS has been adopted as the "gold standard" for the measurement of symptoms of schizophrenia across the world, translated and validated in 40 languages, and used predominantly as an outcome measure for the evaluation of psychopharmacological and non-psychopharmacological treatment interventions in schizophrenia. This presentation will focus on empirical data on the development of the PANSS, its use in clinical trials, the review of the different factor structures reported, item response models and considerations of shortened versions of the PANSS. The scale is a well-established instrument for measuring symptom severity, evaluating 30 separate items, grouped in 7 positive, 7 negative and 16 general psychopathology items. The scale was originally created by merging the 18-item Brief Psychiatric Rating Scale with 12 items from the Psychopathology Rating Schedule. These latter items were essentially added to capture negative symptoms and general psychopathology symptoms. Most items are psychometrically very robust as shown using Item Response Analysis (IRT). We demonstrated that most PANSS items show optimal Option characteristic curves (OCCs) and excellent Item Characteristic Curves (ICCs). Since our original 5-factor model was published many more factor analyses have been published with varying number of factors and varying number of items and with varying levels of goodness of fit data, which will be presented. The widely used Marder model containing all 30 PANSS items, did not perform well as measured by the goodness-of-fit statistics (root mean square error of approximation [RMSEA] and the confirmatory fit index [CFI]). In contrast, our pentagonal model performed well in using only 25 PANSS items in our CFA. The PANSS has also been used as an improvement criterion in clinical trials by using a 20 % improvement rate. This will be discussed in the context of reported correlations with CGI measured improvements. Other developments of the PANSS have included its use as remission criteria, the analysis of the negative symptom subscale into its underlying two-factor structure (expressive and experiential) and the development of the PANSS-derived Excitement scale. Finally, researchers and clinicians have been interested in the development of a shorter version of the PANSS, which would be essentially designed to evaluate response to antipsychotic treatment. Advantages of such a tool would be that it could reduce the burden of the administration of the instrument for patients and raters. There are a few shorter PANSS scales available with a reduced number of original PANSS items, the PANSS-14, PANSS-19 and two shorter versions, the Brief PANSS and the PANSS-6, both including 6 items. The PANSS-6 has been tested up till now quite extensively in established trials and appears to demonstrate high sensitivity to change, and has an established cut off definition for remission. Prospective

testing in new antipsychotic treatment trials is still required for these newer scales. In addition, they need to be supplemented with interview guides and provide conversion formulas to translate total scores from the short PANSS versions to the PANSS-30. Future PANSS scale development needs to address (1) the selection of treatment responsive symptoms by including treatment-sensitive items in a shorter PANSS and (2) illness-phase specific PANSS tools.

Learning Objectives

1. After the presentation, participants will be able to appreciate the psychometric properties of the PANSS as a rating instrument for symptoms of schizophrenia.
2. After the presentation, participants will be familiar with advantages and disadvantages of shorter versions of the PANSS.

Literature References

1. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987; 13:261–276.
2. Santor DA, Ascher-Svanum H, Lindenmayer JP et al. Item response analysis of the Positive and Negative Syndrome Scale. BMC Psychiatr 2007; 7:66.

THE ONCE AND FUTURE PANSS

Mark Opler, MedAvante-ProPhase Inc.

Individual Abstract: Thirty years ago, the Positive and Negative Syndrome Scale (PANSS) was developed to assess the presence and severity of symptoms in psychotic disorders, with the objective of characterizing patients and evaluating change over time. Since the initial publication of the scale, the PANSS has been administered in thousands of clinical trials across the globe to millions of individuals and has been approved by the Food and Drug Administration (FDA) as a primary endpoint for multiple disorders. In the decades since it was published, however, important changes in the clinical research landscape have taken place that necessitate a re-examination of the PANSS. In other words, how well does the PANSS rise to the challenges of the 21st century?

This presentation will review the future challenges facing the use of the PANSS in drug development, observational research, and in community and mental health settings. The future controversies that will be addressed include:

- Can an instrument that was developed during the first wave of atypical antipsychotics provide utility for the second and third generations?
- Does the PANSS meet contemporary standards of patient-centricity and ecological validity?
- Can the PANSS make the leap from research to measurement-based care?
- How will technologies alter the trajectory of PANSS assessments?

In reviewing these questions, we will consider parallel developments, discuss specific case examples, and review the last three decades to provide clues to what the next three decades might hold.

Learning Objectives

1. To understand the strengths and limitations of the PANSS as a tool for clinical research and measure-based care.

2. To evaluate the different development paths and controversies facing the continued use of the PANSS as an instrument for assessment of pathology in patients with schizophrenia and other disorders.

Literature References

1. Yehya A, Ghuloum S, Mahfoud Z, Opler M, Khan A, Hammoudeh S, Hani Y, Al-Amin H. Validation of the Five-Factor Model of the Arabic Version of the Positive and Negative Syndrome Scale in Schizophrenia. Psychopathology. 2017;50(3):211-218.
2. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.

FDA'S INITIATIVES TO OPTIMIZE PEDIATRIC CLINICAL DEVELOPMENT FOR PSYCHIATRIC PRODUCTS

Hao Zhu, U.S. FDA

Overall Abstract A typical pediatric clinical development program for psychiatric products is usually initiated after the product's approval in adults. The program includes multiple trials to obtain the efficacy and safety information in pediatric patients. Under this practice, a few hundred pediatric patients are exposed to the tested product. This approach will lead to a few years of delay for pediatric patients to access a potentially safe and effective treatment with increased cost. In recent years, the division of psychiatry products (DPP) at the food and drug administration (FDA) has taken several initiatives to optimize the pediatric clinical development program of psychiatry products with the objectives to significantly reduce the time and cost for the development program. The proposed three presentations will allow us to share the division's recent effort in streamlining pediatric development program and to seek inputs from the audience.

The first presenter will provide a summary of the current extrapolation strategy to support approval of central nervous system (CNS) stimulant products in adolescents with attention deficit hyperactivity disorder (ADHD). CNS stimulants, such as methylphenidate and amphetamine, have shown to be efficacious in treating ADHD in children, adolescents, and adults. Because of the strong concentration-response relationship, various CNS stimulant products with altered pharmacokinetic (PK) profiles are developed to achieve different clinical responses. Therefore, clinical trials are conducted to obtain the information on the onset and duration of the effect for each product under development. At present, DPP recommends that clinical efficacy assessment be always needed in children. But for some CNS stimulant products, the efficacy findings can be extrapolated to adolescents based on PK bridging without additional clinical efficacy trials. Several products have been approved using this strategy.

The second presenter will share a research aimed to quantitatively describe the clinical outcome change over time in bipolar disorder patients receiving placebo. The findings were based on various well-controlled, double-blinded clinical trials submitted under different new drug applications (NDAs). In addition, the pattern for patients to prematurely discontinued form the trial will also be described. The quantitative description of the trial information allows a detailed comparison of the similarity between pediatric patients and adult patients. Based on the findings from this analysis, different strategies can be explored to allow the findings from adults be extended to support the safe and effective use of the product in pediatric bipolar disorder patients. This project may enable a more efficient clinical develop program in pediatric patients.

The third presenter will discuss the potential to directly extrapolate the efficacy findings for the treatment of schizophrenia from adults into pediatric patients based on PK bridging. To apply this approach, it is essential to demonstrate that the patient response in the placebo and treatment arms are similar between pediatric patients and adults. Multiple clinical trial data in both adult and pediatric patients obtained through NDA submissions will be quantitatively assessed. The results can be shared at the presentation. The proposed approach may significantly reduce unnecessary clinical trials in pediatric patients, and still ensure effective use of the product.

Learning Objectives

1. To share the DPP's current effort on streamlining pediatric clinical development programs for psychiatric products.
2. To seek inputs for further improvement on pediatric clinical development programs for psychiatry products.

CHARACTERIZATION OF PLACEBO EFFECT IN PATIENTS WITH BIPOLAR DISORDER

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

Individual Abstract: Objective: As is true for most neuropsychiatric disorders, clinical trials for bipolar disorder are generally considered to be challenging. One of the challenges is that placebo response varies widely, both within and across clinical trials. This variability in placebo response may be one explanation for the relatively modest drug-placebo differences observed in clinical trials targeting manic symptoms in bipolar patients, which significantly interferes signal detection for new medications and even results in failure of trials. Thus it may be useful to develop a placebo model to quantify the time course of placebo effect across different trials and to identify factors that can explain the heterogeneity in placebo response. Such a model could serve as a valuable drug development tool to help design future clinical trials by providing a quantitative assessment of the expected placebo response in a specific patient population. .

Methods: A disease database was developed including patient-level data from 11 clinical trials targeting manic symptoms in bipolar patients for 5 drugs approved for the acute treatment of manic symptoms in patients with bipolar disorder. Trial selection was driven by availability of electronic datasets containing longitudinal Young-Mania Rating Scale (YMRS) score measurements. The longitudinal YMRS score data were analyzed using nonlinear mixed effect models. The models reported for other neuropsychiatric disorders were first explored as candidate models to describe the time course of YMRS scores. A parametric survival model was utilized to describe the dropout pattern during the trials. Various patient characteristics and trial features were explored as potential covariates to explain the between patient or between-trial variability in dropout patterns. A disease model was developed for the clinical endpoint. In addition, drop-out model was developed to describe the drop-out pattern based on integrated data from multiple clinical trials.

Results: An empirical placebo effect model with an exponential decay process plus a linear progression process was developed to quantify the time course of the YMRS total score based on only placebo data from the database. In order to describe the dropout pattern during the trials, a parametric survival model was developed and the Weibull distribution was identified to be the best distribution to describe the data. Based on the likelihood ratio test, it was found

that patients with higher baseline score, slower disease improvement and more rapid disease progression tended to dropout earlier, and the trial features such as trial starting year and trial site were also significant covariates for dropout..
Conclusions: The joint placebo response and dropout models can serve as a tool to simulate the most likely level of placebo response with the expected dropout pattern to help design a new clinical trial. Similar analysis can be conducted for pediatric trials. The results can be used to assess the similarity of disease progression between pediatric and adult patients. In addition, if exposure-response relationship can also be shown to be similar between the two patient populations, full extrapolation is possible to approve drugs that are already approved for adult population without a dedicated efficacy trial for pediatric population, which will significantly speed up the pediatric program.

Learning Objectives

1. Placebo and drop-out models for bipolar disorder.
2. Clinical trial simulation to optimize pediatric drug development.

Literature References

1. Sun W, Laughren TP, Zhu H, Hochhaus G, Wang Y., Development of a placebo effect model combined with a dropout model for bipolar disorder, J Pharmacokinet Pharmacodyn. 2013 Jun;40(3):359-68.
2. Girgis IG, Nandy P, Nye JS, Ford L, Mohanty S, Wang S, Ochalski S, Eerdekens M, Cox E, Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to <10 years of age, Epilepsia. 2010 Oct;51(10):1954-62.

EXTENSION OF EFFICACY AND SAFETY FINDINGS FROM CHILDREN TO ADOLESCENTS FOR THE TREATMENT OF ATTENTION DEFICIT AND HYPERACTIVITY DISORDER FOR SOME CENTRAL NERVOUS SYSTEM STIMULANT PRODUCTS

Hao Zhu, U.S. FDA

Individual Abstract: Objective: Central nervous system (CNS) stimulants, such as amphetamine and methylphenidate, are widely used for the treatment of attention deficit and hyperactivity disorder (ADHD). Both amphetamine and methylphenidate demonstrate strong concentration-clinical outcome relationships[1, 2]. Multiple formulations containing amphetamine or methylphenidate are designed with the objectives to create the unique drug release mechanism, to yield different pharmacokinetic profiles, and to produce different clinical outcomes. Clinical efficacy and safety trials are generally conducted to obtain the information on the onset and duration of the pharmacodynamic effect, and to ensure safe and effective use of each product. A standard clinical development program includes the assessment of efficacy and safety information in school year children, adolescents, and adults. In recent years, some of the amphetamine and methylphenidate products are approved under a clinical program where efficacy and safety information are mainly obtained in children. Based on the pharmacokinetic bridging, the efficacy and safety findings may be extended to support the approval in adolescents. In this presentation, we plan to share some experience on applying this strategy to support the approval of several methylphenidate and amphetamine products.
Methods: The FDA's recent experience by using pharmacokinetic bridging to support the approval of different amphetamine and methylphenidate products will be shared. The details of the strategy for each product will be presented. In addition, some issues for certain products which may prevent us to apply the strategy will also be discussed.

Results: Through general pharmacology and prior clinical experience, both methylphenidate and amphetamine at the approved exposure range are shown to be safe and efficacious in children, adolescents, and adults. It has been shown that pharmacokinetic profiles for amphetamine and methylphenidate are critical to the unique clinical outcome and safety profiles of each product. Clinical trials are essential to determine the onset and duration of each product. This information may be applied to guide appropriate usage in clinical practice. After the onset and duration is obtained from children, the main disease population, we may extend the findings from children into adolescents without additional clinical trial. If the similarity of pharmacokinetic profiles between children and adolescents can be demonstrated, similar onset and duration of drug effect in adolescents may be implied. This approach has been applied to support the approval of several products, such as Quillichew ®.
Conclusions: The pharmacokinetic bridging approach is based on the general understanding of the pharmacology of central nervous system stimulants. The knowledge and experience from early clinical trials using products with the same active moiety provides additional assurance. The approval of some amphetamine and methylphenidate products based on pharmacokinetic bridging demonstrates the division's recent effort to fine tune pediatric clinical development program. This effort allows us to alleviate the needs to unnecessarily expose to some pediatric patients the test drug. With this expedited program, a product can be developed with less time and reduced cost. In addition, the product can become available to pediatric patients earlier than the old practice.

Learning Objectives

1. To share the DPP's current effort on improving the pediatric clinical development programs for psychiatric products indicated for the treatment of Attention Deficit and Hyperactivity Disorder.
2. To seek inputs for further improvement on pediatric clinical development programs for these programs.

Literature References

1. Li L, Wang Y, Uppoor RS, Mehta MU, Farchione T, Mathis MV, Zhu H. Exposure-response analyses of blood pressure and heart rate changes for methylphenidate in healthy adults.J Pharmacokinet Pharmacodyn. 2017 Jun;44(3):245-262.
2. Kimko H, Gibiansky E, Gibiansky L, Starr HL, Berwaerts J, Massarella J, Wiegand F (2012) 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 (2):161-176.

A MODEL BASED APPROACH TO ESTABLISH DISEASE SIMILARITY IN ADULTS AND ADOLESCENTS WITH SCHIZOPHRENIA

Islam Younis, US Food and Drug Administration

Individual Abstract: Background: While the onset of schizophrenia typically occurs in young adulthood (ages 18 to 25), adolescent onset is not uncommon, with an incidence ranging from 0.1% to 1% in individuals aged 13 to 17 years old. Currently, there are a limited number of antipsychotics approved for the treatment of adolescent schizophrenia. There is an increase in public outcry regarding the enrollment of pediatric patients into placebo controlled trials, thus leading to recruitment challenges and high dropout rates. These potential pitfalls can be

circumvented by extrapolating efficacy from adult data to the adolescent population by assessing similarity in disease and response to therapy. The objective of this study is to utilize a quantitative model based approach to assess of disease similarity in adult and adolescent schizophrenia to support full extrapolation of efficacy.
Method: A disease progression model using subject level placebo data from eight adult (N=3,843) and 5 adolescent (N=387) antipsychotic NDAs in acute schizophrenia, was developed to describe the time course of total positive and negative syndrome scale (PANSS) in adults. Parametric time to event analysis was utilized jointly to describe observed dropout patterns. Various patient characteristics and trial features were explored as potential covariates to explain the between subject variability. The developed and validated joint model was then used to simulate 200 replications of the adolescent data to evaluate disease similarity.
Results: An empirical Weibull model adequately described longitudinal total PANSS in adults with subjects achieving 63.2% of the maximum placebo effect at 3.4 weeks. Baseline total PANSS scores was found to be the only significant covariate suggesting that patients with higher baseline scores exhibited smaller placebo effect. A Weibull distribution was also selected for the dropout model with covariates demonstrating that patients with covariates of higher baseline total PANSS, US trials, patients with minimal changes in total PANSS were more likely to dropout. Visual predictive check of simulated adolescent data using the adult model provided evidence of disease similarity
Conclusion: The use of quantitative disease models provides a novel method for evaluating disease similarity for potential extrapolation of adult data to different populations. Evaluation of exposure response similarity can be subsequently conducted to support full extrapolation. Furthermore, the joint placebo-dropout model can be used to inform future adolescent studies in schizophrenia in the event of partial extrapolation.

Learning Objectives

1. How quantitative methods can be used to establish disease similarity between adults and adolescents.
2. Feasibility of extrapolation of schizophrenia efficacy from adults to adolescents.

Thursday, May 31, 2018

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

KEYNOTE PLENARY: TREATMENT OF PSYCHIATRIC ILLNESS ACROSS THE LIFESPAN

Marlene Freeman, Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health

Overall Abstract: The 2018 ASCP Plenary Keynote Session will address pivotal topics in psychiatry. Dr. Sandra Comer will present on the abuse of opioids, now a well-recognized public health problem in the U.S. She will address this important issue, with a focus on opioid use disorder (OUD) across the lifespan. While OUD is often recognized in younger and middle-aged people, OUD among older individuals has become increasingly common and needs to be better understood. She will describe the incidence and patterns of opioid use across different age groups, as well as the morbidity and mortality associated with the use of opioids

across the lifespan and associated treatment considerations. Dr. Helen Mayberg will discuss the topic of Deep Brain Stimulation (DBS) for treatment resistant depression (TRD). There has been great excitement following initial positive findings, although more recently there have been inconsistent results in clinical trials. It is important in moving forward to understand these contradictory outcomes. Dr. Mayberg will discuss aspects of DBS and neuromodulation that will impact refinement of treatments in this area. She will address translational aspects of treatment development in this area. Dr. John Mann will present on suicide, a crucial public health topic, and discuss implications across the lifespan. He will discuss how suicidal ideation and behavior evolves with age, and he will discuss emerging knowledge of specific risk factors. This information is critical in the development of prevention strategies for different age groups.

OPIOID USE ACROSS THE LIFESPAN

Sandra Comer, Columbia University & New York State Psychiatric Institute

Abstract: Abuse of opioids is now a well-recognized public health problem in the U.S. Opioid use disorder (OUD) is often considered to be an affliction primarily of younger and middle-aged people, but OUD among older individuals has become increasingly common. Little is known, however, about the characteristics of older patients with OUD, as well as the unique risks of opioid use and treatment outcomes in this population. The purpose of the present symposium is to describe the incidence and patterns of opioid use across different age groups, as well as the morbidity and mortality associated with the use of opioids across the lifespan.

Learning Objectives

1. Describe the risk factors associated with opioid misuse across the lifespan.
2. Describe the adverse effects associated with opioid use in older adults.
3. Describe the unique treatment needs among older individuals with OUD.

Literature References

1. Cicero TJ, Surratt HL, Kurtz S, et al: Patterns of prescription opioid abuse and comorbidity in an aging treatment population. J Substance Abuse Treatment 2012; 42: 87-94.
2. Carew AM, Comiskey C: Treatment for opioid use and outcomes in older adults: A systematic literature review. Drug and Alcohol Depend 2018; 182: 48-57.

STRATEGIES TO REFINE AND OPTIMIZE DBS FOR DEPRESSION: A MULTIDISCIPLINARY TRANSLATIONAL APPROACH

Helen Mayberg, Icahn School of Medicine at Mount Sinai

Abstract: It is now more than fifteen years since the first study of Deep Brain Stimulation (DBS) for treatment resistant depression (TRD). While multiple centers, testing this and other targets, have replicated these initial positive findings, pivotal industry clinical trials have proven unsuccessful (2). Strategies to understand these contradictory outcomes are now a priority in the field, particularly with continued interest in development of more advanced invasive neurotechnologies for depression and other treatment refractory neuropsychiatric disorders. Given emerging evidence of sustained long-term positive outcomes despite short term failed trials, a systematic multidisciplinary assessment of variables contributing to the observed response heterogeneity are critically needed. To this end, the refinement of DBS of the subcallosal cingulate (SCC) for TRD is illustrative. Until recently, surgical implantation of DBS electrodes relied on high resolution structural images to localize the SCC grey matter-white matter border followed by trial-and-error behavioral testing of chronic stimulation at

individual contacts. Clinical response however, may be optimized by more precise targeting along specific white matter tracts, as evidenced by recent diffusion tensor imaging and tractography analyses of DBS responders and non-responders. Based on these retrospective findings, standardization of the surgical procedure has now been improved by use of individualized maps to prospectively guide electrode targeting (1). The use of close clinical monitoring and systematic long-term follow-up using small experimental cohorts outside of industry-sponsored trials has further provided new perspectives on the time course, trajectory and sustainability of DBS-mediated effects. Next-generation devices additional allow ongoing recordings of local field potentials during acute and chronic stimulation enabling real-time electrophysiological measurements of the time course, trajectory and sustainability of DBS-mediated antidepressant effects. This strategic integration of combined multimodal neuroimaging, behavioral and neural recordings offers a unique opportunity to link first person experiences to changes in brain state towards a more comprehensive understanding of illness and recovery at the neural level.

Learning Objectives

1. Assess the emerging data on imaging biomarkers that might best guide surgical planning and patient selection for subcallosal cingulate DBS.
2. Appreciate multimodal behavioral, electrophysiological and analytical strategies to define acute and chronic antidepressant effects of subcallosal cingulate DBS.

Literature References

1. Riva-Posse P, Choi KS, Holtzheimer PE, et al. A connectomic approach for SCC DBS surgery: prospective targeting in TRD. Molecular Psychiatry 2017 online April 11.
2. Smart OL, Tiruvadi VR, Mayberg HS. Multimodal Approaches to Define Network. Oscillations in Depression. Biol Psychiatry. 2015 77(12):1061-1070. PMID: 25681871.

SUICIDAL BEHAVIOR ACROSS THE LIFE CYCLE

J. John Mann, Columbia University

Abstract: Suicidal behavior evolves across the life cycle with more nonfatal behavior and more suicide attempts in adolescents and young adults. Death rates remain relatively even from mid-adolescence through mid-life. These differences are paralleled by age-related changes in suicide intent and decision-making. Brain biology tracks with this evolving picture of risk factors. Prevention strategies must be adapted to the age group of at-risk patients.

Learning Objectives

1. To understand how the form of suicidal behavior evolves across the life cycle and its clinical and biological counterparts.
2. To consider the adjustments needed for suicide prevention across the life-cycle.

Literature References

1. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lonnqvist J, Malone K, Marusic, A, Mehlum L, Patton G, Phillips M, Rutz W, Rihmer Z, Schmidtke A, Shaffer D, Silverman M, Takahashi Y, Varnik A, Wasserman D, Yip P, Hendin H. Suicide prevention strategies: a systematic review. JAMA. 2005;294(16):2064-74.

Federal Agency Directors Plenary
10:00 a.m. - 12:30 p.m.

FEDERAL AGENCY DIRECTORS PLENARY SESSION

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

Overall Abstract: Lorenzo Leggio will discuss recent advances and long-term goals of the medications development program at NIAAA. Ivan Montoya will discuss research priorities of NIDA's Medications Development Program. Shelli Avenevoli, representing the NIMH, will discuss updates and research priorities. Lori Davis will speak on the research priorities for the psychopharmacologic treatments of mental disorders at the Veterans Affairs Office of Research & Development. Finally, Dr. Hoover will provide an overview of the Military Operational Medicine Research Program structure and principal areas of research of the Department of Defense.

NIAAA UPDATE

Raye Litten, NIAAA

Abstract: Dr. Lorenzo Leggio 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; and 4) improving the efficiency and methodology of alcohol clinical trials focusing on new treatment endpoints.

Learning Objectives

1. Determine promising compounds to treat alcohol use disorder.

Literature References

1. Litten R. Z., Wilford, BB, Falk DE, Ryan ML, Fertig JB. Potential medications for the treatment of alcohol use disorder: An evaluation of clinical efficacy and safety. Substance Abuse 2016; 37:286-298.

RESEARCH PRIORITIES OF NIDA'S MEDICATIONS DEVELOPMENT PROGRAM

Ivan Montoya, DHHS/National Institute on Drug Abuse

Abstract: The NIDA Medications Development Program was created in 1989 by a mandate from the U.S. Congress. The MDP is located in the Division of Therapeutics and Medical Consequences of Drug Abuse (DTMC). Its mission is to advance the development of medications to treat Substance Use Disorders (SUDs) by supporting the synthesis and pre-clinical evaluation of potential therapeutics, clinical trial design and execution, and preparing regulatory submissions. The Division funds these efforts through peer reviewed grants, contracts, and interagency agreements. Projects focused on cocaine, methamphetamine and marijuana use disorders are a high priority because there are no FDA-approved treatments for these disorders. However, given the current opioid use crisis, the development of medications to prevent and treat opioid use disorders and overdose. The purpose of the presentation is to provide an overview of the medications that are being evaluated in the MDP and describe the funding opportunities that are available at NIDA to support medications development studies.

Learning Objectives

1. At the end of the presentation, the attendees will gain knowledge about the NIDA research priorities and advances in the development of medications to treat Substance Use Disorders.

Literature References

1. NIDA Medications Development Program: https://www.drugabuse.gov/about-nida/organization/divisions/division-pharmacotherapies-medical-consequences-drug-abuse-dpmcda/research-programs.
2. Butelman ER, Kreek MJ. Medications for substance use disorders (SUD): emerging approaches. Expert Opin Emerg Drugs. 2017 Dec; 22(4):301-315. .

NIMH UPDATES AND RESEARCH PRIORITIES

Shelli Avenevoli, National Institute of Mental Health/NIH

Abstract: The National Institute of Mental Health is the lead federal agency for funding of mental health research. The NIMH mission is to transform the understanding and treatment of mental illness through basic and clinical research, paving the way for prevention, recovery and cure. This presentation will provide updates on NIMH research priorities and initiatives related to neuropsychiatric drug development. These include ongoing efforts to address the translational gap between basic and clinical neuroscience; near-term studies addressing issues of target engagement, dose ranging, and domain-focused outcomes; proof of concept studies in which drug treatment is explored as an enhancer of behavioral interventions; and longer term efforts to identify biomarkers that can be applied to select, stratify and/or assess drug effects. In addition, in support of the 2018 meeting theme, priorities and promising findings on the identification and treatment of psychiatric illness across the lifespan will be highlighted.

Learning Objectives

1. At the end of the presentation, the attendees will gain knowledge about

NIMH research priorities and initiatives related to neuropsychiatric drug development.

VA RESEARCH PRIORITIES FOR PSYCHOPHARMACOLOGIC TREATMENTS OF MENTAL DISORDERS

Lori Davis, Veterans Affairs Medical Center

Abstract: The Veterans Affairs Office of Research and Development proudly supports research activities for the advancement of new drug treatments for posttraumatic stress disorder, addictions, and other mental health conditions. The VA research portfolio includes basic science, clinical science, rehabilitation, and health services research. Although VA research programs are intramural, VA is doing more to partner with the pharmaceutical industry and other federal agencies to advance the field of psychopharmacologic treatments. Dr. Davis will give an overview of current VA priorities and initiatives, including the extensive work being done to increase the quality and number of investigators and studies focused on new pharmacotherapies for the treatment of PTSD.

Learning Objectives

1. After attending the panel, participants should be able to list the major research initiatives and priorities of the VA Office of Research and Development.

Literature References

1. Krystal JH, Davis LL, Neylan TC, A Raskind M, Schnurr PP, Stein MB, Vessicchio J, Shiner B, Gleason TD, Huang GD. It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: a consensus statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry. 2017; 82(7):e51-e59.

DEPARTMENT OF DEFENSE MILITARY OPERATIONAL MEDICINE RESEARCH PROGRAM

Ronald Hoover, Department of Defense

Abstract: An overview of the Military Operational Medicine Research Program structure and principal areas of research will be provided, to include a review of research funding mechanisms available to prospective investigators. Additionally, information will be provided describing primary behavioral health challenges within the military, and the need for novel psychopharmacologic solutions for risk mitigation and treatment of Behavioral Heath disorders, to include depression, suicide, post-traumatic stress disorder, and substance abuse. The presentation will include an overview of current psychopharmacologic research efforts addressing these issues.

Learning Objectives

1. Participants should expect to have a general understanding of the Behavioral Health research challenges the Military Operational Medicine Research Program has prioritized, particularly in the area of psychopharmacologic research. Additionally, participants should have knowledge of the research funding opportunities and mechanisms available for submission of research proposals, and how to seek more information if needed.

Literature References

1. McGurk et al. Army Al&T, October-December 2017, pages 68-73.

Clinical Updates in Psychopharmacology*
2:00 p.m. - 3:30 p.m.

CLINICAL UPDATES IN PSYCHOPHARMACOLOGY

Holly Swartz, University of Pittsburgh School of Medicine Department of Psychiatry

Overall Abstract: Dr. Anita Clayton will discuss pharmacologic treatments for sexual dysfunction. Dr. Rajnish Mago will discuss the role of pharmacogenomic testing in clinical decision making. Dr. Anthony Rostain will discuss treatment of ADHD across the lifespan.

PATHOPHYSIOLOGY, ASSESSMENT, AND TREATMENT OF SEXUAL DYSFUNCTION

Anita Clayton, University of Virginia

Abstract: There is a well-established relationship between sexual functioning and quality of life. Sexual disorders appear to be related to hypoactive excitation and/or increased inhibition modulated through CNS and peripheral neuroendocrine systems. A thorough biopsychosocial evaluation is important to identify modifiable factors including medical/psychiatric conditions, hormonal status, contributing medications/substances, relationship difficulties, impact of sexual trauma, restrictive beliefs, etc., and patient preferences which inform treatment.

Interventions include education, effective management of medical/psychiatric conditions, substance/medication discontinuation or change, addition of antidotes, use of hormones and approved agents for sexual dysfunction, and targeted psychotherapy.

Learning Objectives

1. Describe the pathophysiology of sexual dysfunction including modulation of the balance of excitation and inhibition via neuroendocrine systems.
2. Articulate interventions to address modifiable factors and primary sexual dysfunctions.

Literature References

1. Pfaus JG. Pathways of sexual desire. J Sex Med 2009;6(6):1506-1533.
2. Clayton AH, et al. The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women. Mayo Clinic Proceedings. In press (April 2018).

WHICH PHARMACOGENOMIC TESTS ARE USEFUL FOR PREDICTING AND REDUCING ADVERSE EFFECTS?

Rajnish Mago, Simple and Practical Mental Health(simpleandpractical.com)

Abstract: While evidence for the role of genetic polymorphisms in moderating the effects of psychotropic medications continues to increase and several companies are marketing commercial pharmacogenomic tests. Clinicians need to learn more about how data on genetic polymorphisms should or should not be used in clinical practice in 2018. This talk will explain why it is neither true that pharmacogenomic testing can tell us which medications to use nor that such testing "is not ready for prime time." Rather, clinicians need to ask themselves: Which tests, for which persons, for which medications, and in what kinds of situations? This talk will offer a simple and practical introduction to the use of pharmacogenomic tests in selected cases to identify an increased risk of adverse effects and to guide dosing.

Learning Objectives

1. Name three metabolic and transport pathways that are important in the pharmacokinetics of psychotropic medications.
2. Describe how genetic polymorphisms of the cytochrome P450 system can significantly affect the pharmacokinetics of some psychotropic medications.
3. Name three genetic polymorphisms related to the pharmacodynamics effects of psychotropic medications that may significantly increase the risk of adverse effects.
4. Describe the role of HLA testing in psychotropic drug prescribing.

Literature References

1. Bishop JR, Moline J, Ellingrod VL, Schultz SK, Clayton AH. Serotonin 2A -1438 G/A and G-protein Beta3 subunit C825T polymorphisms in patients with depression and SSRI-associated sexual side-effects. Neuropsychopharmacology. 2006 Oct;31(10):2281-8.
2. de Klerk OL, Nolte IM, Bet PM, Bosker FJ, Snieder H, den Boer JA, Bruggeman R, Hoogendijk WJ, Penninx BW. ABCB1 gene variants influence tolerance to selective serotonin reuptake inhibitors in a large sample of Dutch cases with major depressive disorder. Pharmacogenomics J. 2013 Aug;13(4):349-53.
3. Murphy GM Jr, Hollander SB, Rodrigues HE, Kremer C, Schatzberg AF. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine

efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry. 2004 Nov;61(11):1163-9.
4. Murphy GM Jr, Kremer C, Rodrigues HE, Schatzberg AF. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry. 2003 Oct;160(10):1830-5.
5. Zhang JP, Lencz T, Zhang RX, Nitta M, Maayan L, John M, Robinson DG, Fleischhacker WW, Kahn RS, Ophoff RA, Kane JM, Malhotra AK, Correll CU. Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis. Schizophr Bull. 2016 Nov;42(6):1418-1437.

UPDATE ON TREATING ADHD

Anthony Rostain, University of Pennsylvania

Abstract: It is estimated that 5%–8% of school-aged children and 4% of adults in the United States suffer from some form of attention deficit disorder and that the incidence of the disorder is increasing in the population. Although it is the most widely studied behavior disorder of childhood, its etiology remains unclear, its outcome is variable, and its treatment is both complex and moderately successful. Advances in neuroscience have provided new insights into the pathophysiology of ADHD, pointing to key neural circuits involved in attention, behavioral control, learning, and reward maintenance that appear to be underperforming in patients with the disorder. Moreover, the etiology of this heterogeneous disorder points to the key role of genetic x environment interactions during prenatal and perinatal periods. The mainstay of treatment is a multimodal approach combining medications and psychosocial interventions that are tailored to the patient and family's priorities.

This presentation will summarize our current understanding of the neurobiology of ADHD, review the mechanism of action of commonly prescribed ADHD medications, offer practical tips for prescribing and monitoring medications (including when these are combined with other psychopharmacologic agents), and describe new medication options currently under investigation.

Learning Objectives

1. Current understandings about the neurobiology of ADHD.
2. Mechanisms of action of commonly prescribed ADHD medications.
3. Practical tips for prescribing and monitoring medications.
4. New medication options currently under investigation.

Literature References

1. Fredrikse,n M., Halmoy, A., Faraone, S.V. & Haavik, J. "Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: A review of controlled and naturalistic studies." European Neuropsychopharmacology 23:508-527, 2013.

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

PROBLEMS AND IMPLEMENTATIONS OF CNS CLINICAL TRIALS

John Newcomer, Charles E. Schmidt College of Medicine, Florida Atlantic University

Overall Abstract: This workshop will focus on issues that CROs face, including problems and implementation of CNS clinical trials. John Kane will be discussing diagnostic and assessment challenges in the design and conduction of clinical trials. Penny Randall will then discuss leveraging new tools available for industry in CNS trials. Daniel Burch will then discuss becoming more clever, inclusive, and broader with patient selection including relying on data for patient selection and matching sites. Finally, George Papakostas will discuss placebo response and expectancy.

Learning Objectives

1. Discuss how telemedicine can drive greater efficiencies in clinical research, including expanded access to new sources of trial subjects and decreasing trial burden of subjects.
2. Summarize the telemedicine pilot findings including the evaluation of data quality (endpoint validation).

DIAGNOSTIC AND ASSESSMENT CHALLENGES IN THE DESIGN AND CONDUCTION OF CLINICAL TRIALS

John Kane, The Zucker Hillside Hospital

Individual Abstract: Clinical trials are a critical component in the development of new treatments in CNS disorders. Given the lack of biomarkers and the subjective nature of many psychiatric symptoms the processes involved in collecting outcome data becomes critical.
In addition, misaligned incentives can provide an additional challenge when study conduct is reimbursed on a per patient enrolled basis.
In recent years there has been an increasing effort to enhance the reliability and validity of assessment methods by utilizing third parties to review assessments, conduct centralized assessments or utilize new technologies to enhance data quality. Unfortunately, there has been little systematic research comparing the effectiveness of different strategies and seemingly no sponsor, either governmental or private, is willing to take on this challenge.
This presentation will provide an overview of these issues and discuss potential strategies for making further progress.

Learning Objectives

1. To provide the audience with knowledge as to different methods for facilitating reliability and validity assessments in clinical trials.
2. To discuss how factors such as inter-rater reliability influence signal detection in clinical trials.

Literature References

1. Kobak K, Kane JM, Thase ME, Nierenberg AA. Why do clinical trials fail? The problem of measurement error in clinical trials: time to test new paradigms? J Clin Psychopharm. 27(1):1-5, 2007.
2. Alphs L, Bossie C, Serpico S, Benedetti F, Fleischhacker W, Kane JM. Placebo-related effects in clinical trials in schizophrenia: what is driving this phenomenon and what can be done to minimize it. Intl Journal of Neuropsychopharmacology 15(7):1003-14, 2012.

A TELEMEDICINE PROOF OF CONCEPT STUDY EVALUATING THE REMOTE DETECTION OF ALZHEIMER'S DISEASE AND CATEGORIZATION OF SEVERITY

Penny Randall, IQVIA

Individual Abstract: Purpose: Frequently, MCI due to AD patients are undiagnosed in this early stage of their illness and unfortunately are not presented the opportunity to participate in clinical trials. The current practice in running AD trials relies on expert CNS investigative sites. Yet, early stage dementia patients are far more likely to be treated by their primary care physicians for chronic illnesses rather than to be under the care of expert in neurodegenerative diseases for cognitive symptoms.
Methodology: The proof-of-concept, Phase II trial (REINVENT, NCT 02778438) involved using a site research network comprised of primary care research physicians (spoke sites) linked via a telemedicine platform to an expert Alzheimer's disease investigative site (hub site). This hub and spoke structure allowed IQVIA to expand our reach into a difficult to access population—MCI due to AD. By taking the trial directly to the patient or recruiting subjects directly where receive health care services are delivered, from primary care physician practices or spoke sites, we looked to access a new patient pool.
The hub site is a CNS AD expert site with experience in conducting AD studies and knowledgeable staff, (a PI and sub-Investigators and CNS raters) to provide the specialized knowledge to diagnose and to rate symptom severity on standard AD assessments.
Another important component of the study was focused on endpoint validation, demonstrating that the remote collection of key Alzheimer's disease outcome measures was reliable and of comparable quality to standard face-to-face ratings.
Results: Remote screening of subjects from primary care practices yielded brisk recruitment. On average, over 20 patients were screened and eight patients enrolled per month, which is a rate far higher than studies targeting a similar stage of disease. Additionally, the endpoint validation work showed strong correlation between remotely rated cognitive assessments compared to standard, face-to-face ratings (ICC 0.79-0.92). Importantly, feedback from both study subjects and their caregivers/partners was positive about participating in the remote visits for this trial.
Importance of Proposed Talk: This successful proof-of-concept virtual trial provided rich knowledge in applying new technologies to clinical development.
By bringing the trial directly to the patient through a virtual platform, the burden of trial participation is reduced for patients and their families, which in turn accelerates recruitment and timelines while reducing development costs.

Learning Objectives

1. Discuss how telemedicine can drive greater efficiencies in clinical research, including expanded access to new sources of trial subjects and decreasing trial burden of subjects.
2. Summarize the telemedicine pilot findings including the evaluation of data quality (endpoint validation).

Literature References

1. Herbert et al.,(2003): Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003 Aug; 60 (8):1119-22.
2. Amengual, T et al., (2016): Rare Disease Clinical Research: Caregivers' Perspectives on Barriers and Solutions for Clinical Research Participation." Neurology April 5, 2016 vol. 86 no. 16 Supplement I8.001.

BECOMING MORE CLEVER, INCLUSIVE, AND BROADER WITH PATIENT SELECTION INCLUDING RELYING ON DATA FOR PATIENT SELECTION AND MATCHING SITES

Daniel Burch, PPD

Individual Abstract: According to the Center for Information and Study on Clinical Research Participation (CISCRP), planned CNS study duration has increased by 116%, in order to reach target patient enrollment. While patients' willingness to participate tends to be high, study awareness is uneven, at best. Fortunately, practical options exist for ameliorating delays without sacrificing quality. In this session, we'll discuss effective means for building awareness in underserved populations, strategies for matching patients to the sites that are best suited to serve them, as well as patient-site communications methodologies that enhance enrollment and retention.

Learning Objectives

1. Legacy Barriers and Primary Elements of Engagement.
2. Rethinking Barriers to Participation.

Literature References

1. https://www.ciscrp.org/download/2017-perceptions-insights-study-the-participation-experience/?wpdmdl=8770.

PLACEBO RESPONSE AND EXPECTANCY

George Papakostas, Massachusetts General Hospital

Individual Abstract: Psychiatric treatment development has traditionally been hampered by relatively high rates of, so called, "failed" trials. Though "negative" trials (in which it can be concluded with confidence that the experimental treatment is not superior in efficacy to placebo) are informative, failed trials (in which there is a high likelihood that the study, either by design or circumstance, was unable to detect a treatment difference from placebo) are, largely, inconclusive. Failed trials represent significant headwinds in treatment development in Psychiatry, because they can erroneously lead to the decision to prematurely end the investigative pursuit of otherwise potentially efficacious therapies. Therefore, it is imperative that we further increase our understanding of factors which influence signal detection in Psychiatric clinical studies. Several elements have emerged that seem to play a critical role in trial success, gradually reshaping the design of clinical, translational, as well as mechanistic studies in the field. In the present session, we will discuss potential implications of subject and investigator expectations on clinical trial recruitment and outcome.

Learning Objectives

1. By the end of this session, attendees will better understand the relationship between subject expectations and clinical trial outcome and recruitment in Psychiatric disorders.
2. By the end of this session, attendees will better understand the relationship between investigator expectations and clinical trial outcome and recruitment in Psychiatric disorders.

Literature References

1. Papakostas, G.I., Østergaard, S.D., Iovieno, N. (2015). The nature of placebo response in clinical studies of major depressive disorder. Journal of Clinical Psychiatry, 76(4), 456-66.
2. Papakostas, G.I., Fava, M. (2009). Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. European Neuropsychopharmacology, 19(1), 34-40.

WOMEN'S MENTAL HEALTH ACROSS THE LIFESPAN: KNOWLEDGE GAINED AND EVIDENCE GAPS*

Susan Kornstein, Virginia Commonwealth University

Overall Abstract: This workshop will provide an update on the expanding field of women's mental health across the lifespan, including: 1) discussion of enhanced knowledge of the underpinnings of the relationship between female reproductive biology and risk for psychiatric disorder; and 2) description of the safest and evidenced-based treatments for depression during critical times such as pregnancy and the transition to menopause. Specifically, Dr. Jennifer Payne will give an overview of the genetics of postpartum depression. Dr. Lee Cohen will summarize the challenges of treating depression and bipolar Illness during pregnancy, given the growing amounts of information derived from recent studies of reproductive safety. Dr. Marlene Freeman will address the understudied area of depressive relapse in women pursuing treatment for infertility. Dr. Susan Kornstein will present new guidelines for evaluation and management of depression in the menopause transition. Finally, Dr. Anita Clayton will introduce a new algorithm for the assessment and treatment of hypoactive sexual desire disorder. Discussion will follow.

Learning Objectives

1. The relationship between female reproductive biology and risk for psychiatric disorder.
2. Assessment and treatment of depression related to reproductive events including pregnancy, infertility, and the menopause transition.

UPDATE ON THE GENETIC BASIS OF POSTPARTUM DEPRESSION

Jennifer Payne, Johns Hopkins School of Medicine

Individual Abstract: Objective: To review and summarize the literature exploring the genetic basis for postpartum depression (PPD).
Methods: We undertook a qualitative review of the literature exploring the genetic basis for PPD including familial analyses, linkage and association studies, candidate gene studies and epigenetic biomarker studies.
Results: Evidence is strong for the genetic basis for PPD, with positive associations found in family studies and in several genes associated with Major Depression (including the serotonin transporter, Catechol-O-methyl transferase, and Monoamine Oxidase genes) as well as genes involved in estrogen signaling (including the Estrogen receptor 1 gene) but only when PPD is defined by onset shortly after delivery. Epigenetic biomarkers on genes responsive to estrogen have also been found to predict PPD. One gene identified through a genome-wide linkage and association study, HMCN1, has been replicated in a candidate gene study. Results of a replication cohort examining the association between HMCN1 and estrogen receptor 1 polymorphisms and PPD (currently pending) will also be reported.

Conclusions: Our findings underscore the need for additional studies with larger samples, as well as the crucial importance of timing in the definition of PPD for genetic studies. Future directions will be discussed.
Acknowledgements: K23 MH074799-01A2, 1R01MH104262-01, R01 MH112704-01

Learning Objectives

1. Name two genes that have demonstrated association with postpartum depression.
2. Discuss the role of timing of onset of postpartum depression in the genetic basis for postpartum depression.

Literature References

1. Mahon PB, Payne JL, MacKinnon DF, Mondimore FM, Schweizer B, Jancic D, NIMH Genetics Initiative Bipolar Disorder Consortium, BiGS Consortium, Crowe RP, Coryell WH, Holmans PA, Knowles JA, Scheftner WA, Weissman MM, Levinson DF, DePaulo JR, Zandi PP, Potash JB. Genome-wide linkage and follow-up association study of postpartum mood symptoms. American Journal of Psychiatry. 2009; 166 (11): 1229-1237.
2. Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky Z. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. Molecular Psychiatry. 2013; 19(5):560-7.

TREATING DEPRESSION AND BIPOLAR ILLNESS IN PREGNANCY: KNOWNS AND UNKNOWNS

Lee Cohen, Massachusetts General Hospital

Individual Abstract: The pharmacologic treatment of mood disorders during pregnancy requires a careful weighing of known and unknown risks of fetal exposure to psychotropics such as antidepressants and mood stabilizers. The last two decades have brought numerous reports regarding the reproductive safety of psychiatric medications ranging from analyses of administrative databases to prospective data from medication registries designed to evaluate risk for major malformations and other relevant neonatal and developmental outcomes. Despite the vast accumulation of data regarding the known risks of fetal exposure to certain medications used to treat psychiatric disorder such as major depression and bipolar disorder, the ability to absolutely quantify risks for patients maintained on psychotropics who are planning to conceive is still not absolutely quantifiable. This presentation will review available reproductive safety data regarding the spectrum of medications used to manage major depression and bipolar disorder during pregnancy. Treatment algorithms for management of both of these conditions will be presented as will a model for providing perinatal psychiatric consultation which takes into account those factors which may most inform treatment as women weigh relative treatment options before and during pregnancy.

Learning Objectives

1. Understand critical research findings in course of psychiatric disorder during pregnancy.
2. Recognize the current knowledge gaps in reproductive neuroscience.
3. Receive an update regarding reproductive safety of psychiatric medication during pregnancy.

Literature References

1. Cohen LS, Viguera AC, McInerney KA, Freeman MP, Sosinsky AZ, Moustafa D, Marfurt S, Kwiatkowski MA, Murphy SK, Farrell AM, Chitayat D, Hernandez-Diaz S. Reproductive Safety of Second Generation Antipsychotics: Current Data from the MGH National Pregnancy Registry for Atypical Antipsychotics. American Journal of Psychiatry; 2016 Mar 1; 173 (3): 263-270.
2. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughead A, Vitonis AF, Stowe ZN: Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006; 295(5):499-507.

RISK OF DEPRESSIVE RELAPSE IN WOMEN PURSUING INFERTILITY TREATMENT

Marlene Freeman, Massachusetts General Hospital, Ammon-Pinizzotto Center for Women's Mental Health

Individual Abstract: Women are at a higher risk of experiencing major depressive disorder (MDD) than men, particularly during the reproductive years, with a lifetime risk of MDD of approximately 21%[1]. Infertility affects up to 17% of women aged 20-44 who have partners, and 42-76% of those affected seek infertility treatment in developed countries [2] [3]. Despite the high prevalence of mood disorders among women and that of infertility, there has been a paucity of systematic data to inform the treatment of women at risk for psychiatric morbidity in the context of assisted reproductive technologies (ART). Treatment for infertility is often experienced as a chronic stressor, which may raise the risk of new onset depression or depressive relapse in at-risk women. Unsurprisingly, a history of MDD is associated with a depressive episode during infertility treatment [4], but risk factors for depressive relapse during infertility treatment have received little study. Data on the course of bipolar depression during infertility treatment are also sparse. It is possible that untreated MDD experienced by women undergoing infertility treatment could affect fertility rates through stress-related hormonal dysregulation [5]. Notably, emotional distress has been recognized as a primary reason for discontinuation of infertility treatment in women without a history of psychiatric disorders [6]. Preliminary findings related to depressive relapse in a prospectively followed cohort of women pursuing infertility treatment will be presented. In addition to understanding the comparative risk of depressive relapse between women who maintain or discontinue antidepressant pharmacotherapy while pursuing ART, it is important to identify women with histories of mood disorders at high risk of depressive relapse during ART so that appropriate interventions might be developed to mitigate such risk.

Learning Objectives

1. To understand the prevalence of infertility among women of reproductive age.
2. To understand the clinical context of ART and potential variables associated with depressive relapse in women with histories of MDD.

Literature References

1. Burt, V.K. and K. Stein, Epidemiology of depression throughout the female life cycle. J Clin Psychiatry, 2002. 63 Suppl 7: p. 9-15.
2. Boivin, J., et al., International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod, 2007. 22(6): p. 1506-12.

3. Kessler, R.C., et al., Sex and depression in the National Comorbidity Survey I: lifetime prevalence, chronicity and recurrence. J Affect Disorders, 1993. 29: p. 85-96.
4. Holley, S.R., et al., Prevalence and predictors of major depressive disorder for fertility treatment patients and their partners. Fertil Steril, 2015. 103(5): p. 1332-9.
5. Young, E.A. and A. Korszun, The hypothalamic-pituitary-gonadal axis in mood disorders. Endocrinol Metab Clin North Am, 2002. 31(1): p. 63-78.
6. Van den Broeck, U., et al., Reasons for dropout in infertility treatment. Gynecol Obstet Invest, 2009. 68(1): p. 58-64.

NEW GUIDELINES FOR EVALUATION AND TREATMENT OF DEPRESSION IN THE MENOPAUSE TRANSITION

Susan Kornstein, Virginia Commonwealth University

Individual Abstract: A task force was recently formed by the National Network of Depression Centers and the North American Menopause Society to develop guidelines for the assessment and management of depression in the menopause transition. This talk will discuss the recommendations of the task force regarding diagnostic assessment and treatment considerations. The menopause transition is a period of vulnerability for the development of both depressive symptoms and major depressive episodes. Depression during the menopause transition presents with classic depressive symptoms, usually in association with menopause-specific symptoms and psychosocial stressors. Depressive and menopause-related symptoms may overlap and compound each other. Treatment approaches for depression during the menopause transition include antidepressants, estrogen therapy, psychotherapy, and other modalities. Antidepressants are the first-line treatment choice and may also be beneficial for vasomotor symptoms. Among the antidepressants, only desvenlafaxine has been studied and proven efficacious in large randomized placebo-controlled trials of well-defined peri- and postmenopausal women with major depressive disorder. Estrogen therapy has been shown to be efficacious for perimenopausal (but not postmenopausal) depression, although the data are limited.

Learning Objectives

1. The epidemiology, presentation, and differential diagnosis of depression in the menopause transition.
2. Options for the treatment of depression in peri- and postmenopausal women.

Literature References

1. Maki PM, Kornstein SG, Joffe H, Bromberger JT, Freeman EW, Athappily G, Bobo WV, Rubin LH, Koleva HK, Cohen LS, and Soares CN on behalf of the Board of Trustees for the North American Menopause Society and the Women and Mood Disorders Task Force of the National Network of Depression Centers. Guidelines for the evaluation and treatment of depression in perimenopausal and postmenopausal women: Summary and recommendations. Menopause, in press.
2. A pooled analysis of the efficacy and safety of desvenlafaxine for the treatment of perimenopausal and postmenopausal women with major depressive disorder.
3. Kornstein SG, Clayton (eds). Women's Mental Health. Psychiatric Clinics of North America, volume 40, number 2, June 2017.

HYPOACTIVE SEXUAL DESIRE DISORDER: AN ALGORITHM FOR ASSESSMENT AND INTERVENTION

Anita Clayton, University of Virginia

Individual Abstract: The International Society for the Study of Women's Sexual Health (ISSWSH) developed a Process of Care (POC) algorithm for the management of Hypoactive Sexual Desire Disorder (HSDD) in women. The guideline starts with the provider initiating a discussion about sexual concerns, screening for low sexual desire and associated distress (e.g. with a questionnaire), and distinguishing between generalized, acquired HSDD and other forms of low sexual interest. A biopsychosocial assessment of potentially modifiable factors facilitates initiation of treatment with education and management of these factors such as relationship problems, co-morbid other sexual dysfunctions or medical/psychiatric conditions, and contributing substances/medications. If there are no modifiable factors, or they have been addressed and the HSDD continues, additional therapeutic interventions may be indicated including psychotherapy and prescription drug treatments, guided in part by menopausal status. Finally, scheduled follow-up and assessment of adverse effects and the progress of therapy is recommended.

Learning Objectives

1. Screen for sexual dysfunctions in women to identify hypoactive sexual desire disorder (HSDD), and perform a biopsychosocial assessment for potential etiologies in pre- and postmenopausal women.
2. Describe the available therapeutic interventions for HSDD related to menopausal status.

Literature References

1. Clayton AH, Goldstein I, Kim NN, et al. The International Society for the Study of Women's Sexual Health process of care for management of hypoactive sexual desire disorder in women. Mayo Clinic Proceedings. In Press. April 2018.
2. Parish S, Goldstein A, Goldstein S, Goldstein I, Pfaus J, Clayton AH, et al. Toward a more evidence-based nosology and nomenclature for Female Sexual Dysfunctions-Part II. The Journal of Sexual Medicine 2016;13(12):1888-1906.

BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: PERSPECTIVES IN CLINICAL DEVELOPMENT FROM THE DIVISION OF PSYCHIATRY PRODUCTS, FOOD AND DRUG ADMINISTRATION*

Javier Muniz, Food and Drug Administration

Overall Abstract: As life expectancy lengthens and a larger number of Americans are diagnosed with dementia, the condition's impact is an increasingly important public health concern in the United States. Although most drug development has focused on treating cognitive impairment, the behavioral (e.g., aggression, restlessness, agitation, etc.) and psychological (e.g., depression, anxiety, delusions, etc.) symptoms in dementia negatively affect patients' quality of life and drive a significant portion of the financial, systemic, and caregiver burdens associated with the disease.

Accordingly, in recent years, the FDA's Division of Psychiatry Products has seen an increased interest in developing treatments for behavioral and psychological symptoms in dementia (BPSD). While the Division considers BPSD as legitimate targets for drug development, there are significant challenges in how to select appropriate treatment indications and conduct clinical trials to support regulatory approval.

In this workshop, we will highlight several areas of active dialogue between academia, industry, and regulatory agencies. First, we will discuss three major foci of BPSD: agitation/aggression, psychosis, and apathy. The presentations will describe issues related to characterizing these behavior and symptom clusters, identifying appropriate patient populations, selecting well-defined and reliable clinical outcome measures, and designing clinical trials to demonstrate therapeutic benefit. We will also explore the evaluation of caregiver burden as a potentially acceptable outcome measure. Finally, we will discuss risk/benefit determination to support the approval of novel treatments for BPSD in the target population.

Learning Objectives

1. Attendees will be familiar with major symptoms clusters in BPSD, to include agitation, apathy, and psychosis.
2. Attendees will familiarize with potentially acceptable primary and secondary endpoints for these symptoms clusters (e.g., agitation, apathy).

BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: TREATMENT OF AGITATION

Nancy Dickinson, FDA

Individual Abstract: Agitation in patients with dementia is one of the leading reasons for which patients are institutionalized, often due to caregiver burden. Untreated agitation leads to excess morbidity, mortality, and hospital stays, and may account for up to thirty percent of the cost of maintaining a community-dwelling patient with dementia. Non-pharmacologic treatments may have some effectiveness and should always be first-line treatment for agitation. However, when pharmacologic intervention is necessary, available psychotropic medications studied (but not approved) for agitation have well-documented adverse effects and limited or unknown efficacy. There is an unmet need for Food and Drug Administration-approved medications for treatment of agitation in dementia.

The Division of Psychiatry Products has accepted the International Psychogeriatric Association's provisional consensus definition of agitation in dementia for the purpose of clinical trials. During this talk, we will discuss clinical trial designs for the treatment of agitation, to include patient selection and appropriate endpoints for a potential indication. Agitation assessment scales such as the Cohen-Mansfield Agitation Inventory, the Neuropsychiatric Inventory, and others offer assessment of the three types of agitation behaviors derived from the International Psychogeriatric Association's definition of agitation; we will present the Division's perspective on the utility of these endpoints in clinical trials.

These issues will be of potential interest to sponsors and investigators who are developing treatments for agitation for marketing approval.

Learning Objectives

1. Participants will be able to discuss pharmacologic treatments, clinical trial design, patient population, and endpoint assessments for agitation in dementia.
2. Participants will be able to discuss the FDA views on drug development in this area.

Literature References

1. Livingston, G., Kelly, L., Lewis-Holmes, E., et. al. Non-pharmacological interventions for agitation in dementia: systematic review of randomized controlled trials. The British Journal of Psychiatry (2014) 205, 436-442.
2. Cummings J, Mintzer J, Brodaty H, et. al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. International Psychogeriatrics. (2014) Oct 14,1-11.

APATHY IN DEMENTIA: A CLINICALLY MEANINGFUL TREATMENT TARGET?

Jean Kim, FDA/CDER/DPP

Individual Abstract: Apathy as a behavioral syndrome has been an ongoing topic of study for neuropsychiatric researchers, across multiple psychiatric illnesses including depression, attention-deficit hyperactivity disorder, and schizophrenia . Neuroimaging study results point to a possible common neurocircuitry behind apathy; this neurocircuitry may be particularly vulnerable to and damaged by neuropathological processes in multiple forms of dementia. Recently, researchers and clinicians have conjectured that apathy may be an underrated and understudied contributing factor to poor clinical outcomes in dementia, and that treatment of apathy may in turn improve those outcomes. Preliminary small-scale clinical research trials are already underway to examine apathy as a therapeutic target in dementia. However, as yet, there remains a lack of consensus definitions on the apathy syndrome (i.e., how to parse out its cognitive, affective, and behavioral dimensions, or distinguish it from its clinical cousin anhedonia), and insufficient evidence on whether improvement in apathy can be accurately measured and/or correlated with clinical improvement in dementia. There remain ongoing concerns about how to distinguish apathy's contribution to dementia versus other comorbid syndromes like depression, or from the overall cognitive deficits inherent to progressive dementia. This talk will discuss goals from a regulatory perspective for determining whether apathy is a worthwhile therapeutic target for drug development.

Learning Objectives

1. Participants will be able to learn an overview of current academic research and thought on apathy in dementia.
2. Participants will be able to discuss the FDA's views on future drug development directions in this area.

Literature References

1. Clarke DE, Ko JY, et al. Are the available apathy measures reliable and valid? A review of the psychometric evidence. J Psychosom Res 2011; 70(1):73-97.
2. Lanctot KL, Chau SA, et al. Effect of methylphenidate on attention in apathetic AD patients in a randomized, placebo-controlled trial. Int Psychogeriatr 2014; 26(2):239-246.
3. Lanctot KL, Aguera-Ortiz L, et al. Apathy associated with neurocognitive disorders: recent progress and future directions. Alzheimer's and Dementia 2017; 13:84-100.

DEMENTIA-RELATED PSYCHOSIS: A REGULATORY PERSPECTIVE

Bernard Fischer, U.S. Food and Drug Administration

Individual Abstract: Psychosis is a prominent component of behavioral and psychological symptoms of dementia (BPSD). Dementia, or major neurocognitive disorder (per DSM-5), has many causes including Alzheimer's disease, Lewy body disease, frontotemporal degeneration,

HIV infection, and vascular disease. The nature of psychosis is not uniform in these diseases. Psychosis in frontotemporal degeneration has been mistaken for late-onset schizophrenia. In contrast to schizophrenia, delusions in Alzheimer's disease are not usually bizarre or complex and visual hallucinations are common. Regardless of disease type, psychosis in dementia is associated with poor functional prognosis, high rates of institutionalization, and health problems. It is also associated with agitation and aggression. Indeed, almost all investigations into the nature and treatment of psychosis in dementia have combined the symptoms of psychosis and agitation in their endpoints. The Division of Psychiatry Products is encouraging Sponsors to develop drugs for this unmet need by examining differential response rates in different disease entities, separating psychosis from agitation when designing endpoints, and considering strategies other than dopamine receptor antagonism. This talk will discuss the regulatory aspect of these drug development issues in greater detail.

Learning Objectives

1. Participants will be able to discuss how previous drug development for psychosis in dementia has focused on dopamine receptor antagonists and conflated agitation and psychosis.
2. Participants will be able to discuss the FDA views on drug development in this area.

Literature References

1. Galimberti D, Dell'Osso B, Altamura AC, Scarpini E. Psychiatric symptoms in frontotemporal dementia: Epidemiology, phenotypes, and differential diagnosis. Biol Psychiatry 2015; 78:684-92.
2. Murray PS, Kumar S, DeMichele-Sweet MA, Sweet RA. Psychosis in Alzheimer's disease. Biol Psychiatry 2014; 75(7):542-52.

BENEFIT-RISK DETERMINATION FOR TREATMENTS OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Michael Davis, US Food and Drug Administration

Individual Abstract: In 2005, the Food and Drug Administration issued a public health advisory communicating that treating behavioral disorders in elderly patients with dementia with atypical antipsychotics is associated with increased mortality. This finding, broadened to include typical antipsychotics in 2008, led to the addition of a boxed warning to all antipsychotic labels; this warning describes the class mortality risk and notes that the products are not approved for the treatment of dementia-related psychosis. There are currently no drugs approved for the treatment of BPSD in the United States and, given their negative impact on patients' quality of life, this therapeutic area represents an important unmet medical need.

When reviewing a New Drug Application (NDA) for marketing approval, the FDA must determine whether the drug is effective and whether its benefits outweigh its risks to the patient population. This assessment is currently documented in a benefit-risk framework encompassing five dimensions: analysis of the clinical condition, current treatment options, benefit, risk, and risk management. In this presentation, we will discuss the benefit-risk framework in the context of BPSD and related issues in clinical trial design.

Specific considerations that will be discussed include:

- How do BPSD affect patients' functioning or quality of life?

- How effective are other treatments (including off-label and non-pharmacological therapies) that are used to treat the condition, and how should they be integrated in clinical trials?
- How should clinical meaningfulness be assessed, in terms of benefits to the overall population or to specific subsets of patients?
- How serious are the safety concerns identified in the development program, and what degree of remaining uncertainty is acceptable regarding safety concerns?
- Can we assume that all medications in a heterogeneous class, such as atypical antipsychotics, will carry the same safety risks?
- Are there any strategies that can mitigate the safety concerns adequately to support approval and enable safe product use?

Discussion of these issues will convey the Division's current thinking and help guide future drug development in this therapeutic area.

Learning Objectives

1. Learn the history of the antipsychotic boxed warning for elderly patients with dementia-related psychosis.
2. Understand the FDA's benefit-risk framework for drug approval, using the therapeutic area of BPSD as an example.

Literature References

1. Salzman C, Jeste DV, Meyer RE, Cohen-Mansfield J, Cummings J, Grossberg GT, et al. Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. J Clin Psychiatry. 2008;69(6):889-98.
2. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry. 2015;72(5):438-45.

BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: ASSESSING CAREGIVER BURDEN AS A TREATMENT OUTCOME

Wen-Hung Chen, Center for Drug Evaluation and Research, Food and Drug Administration

Individual Abstract: As life expectancy lengthens and a larger number of Americans are diagnosed with dementia, the condition's impact is expected to become an increasingly important public health concern in the United States. At the front of the impact are the families and friends who provide direct care for an estimated 5 million dementia patients in the United States.

It is important to recognize that dementia not only affects the patients, but also their families and their caregivers who provide direct daily care. Caring for patients with dementia is particularly demanding and the needs for care escalate with the progression of the disease. Caregivers are subject to enormous stress and are at high risk for depression and other health problems. Studies have found caregivers often show symptoms of anger, social withdrawal, anxiety, depression, fatigue, sleeplessness, and cognitive impairment. Caregivers also show increased utilization of health services and psychotropic medications.

The dementia patient's behavioral and psychological symptoms often aggravate the caregiver's distress. Such stress can be harmful to both caregivers as well as the patients. Caregiver burden

is associated with increased likelihood of patients being placed in a nursing home and could be considered as an important target for successful interventions. However, this is a highly complex and controversial issue. At the core of the debate is how does benefit for the caregiver translate to benefit for the patient. This presentation aims to open the dialogue and to invite all stakeholders including caregivers, clinicians, sponsors, payers, regulators, ethicists, and even patients themselves to join the discussion.
If we are to accept caregiver burden as an endpoint in clinical trials, we must first be able to define and measure it. Specifically, we must ensure that the concepts assessed in the measure are direct impacts associated with caring for the patients and that changes in the endpoint are tied to the changes in the patient's condition? The adequacy of the instrument, whether existing, modified, or newly developed, as a measure to assess treatment benefit depends on whether its conceptual framework, content validity, other measurement properties, and interpretation of score are satisfactory in its context of use. A roadmap for patient-focused outcome measurement in drug development will be presented.

Learning Objectives

1. Understand stakeholder perspectives and regulatory considerations on the role of caregiver burden in drug development programs for treatment of dementia.
2. Understand FDA's considerations on developing a well-defined and reliable measure for assessing caregiver burden.

Literature References

1. Mohamed, S., Rosenbeck, R., Lyketsos, C., Schneider, L.S., 2010. Caregiver burden in Alzheimer disease: cross-sectional and longitudinal patient correlates. Am. J. Geriatr. Psych. 18 (10), 917–927.
2. US Food and Drug Administration Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Rockville, MD: Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2009.

LEADERSHIP SKILLS FOR MID-CAREER PROFESSIONALS

Mark Rapaport, Emory University School of Medicine

Overall Abstract: Dr. Peter Topping is our guest presenter for this very special mid-career leadership and career mentoring workshop. Dr. Topping is from the department of Practice of Organization and Management at the Roberto C. Goizueta Business School at Emory University in Atlanta and he has a secondary appointment in the Emory School of Medicine. Dr. Topping will begin the workshop with an inspirational opening talk on leaders at all levels in scientific environments of academia and industry. Drawing from his book entitled Managerial Leadership, he will discuss cognitive approaches to dealing effectively with paradox and contradictions. Using emotional quotient (EQ) as a framework, he will explore how to apply EQ when building relationships with difficult people and how to adapt your leadership style within entrenched cultural settings. Dr. Rapaport and Davis will help spark discussion and Q&A. Dr. Topping looks forward to audience participation to make this workshop dynamic and interactive.

Learning Objectives

1. After the workshop, the participant will be able to dialogue with an advanced understanding of aspects of effective leaders at all levels in scientific environments of academia and industry.
2. After the workshop, the participant will be able to explain cognitive approaches to dealing effectively with paradox and contradictions.
3. After the workshop, the participant will be able to contribute more effectively to building relationships with difficult people and adapt his/her leadership style to advance within entrenched cultural settings.

Friday, June 1, 2018

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

OPTIMIZING SIGNAL DETECTION IN PSYCHIATRIC CLINICAL TRIALS
George Papakostas, Massachusetts General Hospital

Overall Abstract: Psychiatric treatment development has traditionally been hampered by relatively high rates of, so called, "failed" trials. Though "negative" trials (in which it can be concluded with confidence that the experimental treatment is not superior in efficacy to placebo) are informative, failed trials (in which there is a high likelihood that the study, either by design or circumstance, was unable to detect a treatment difference from placebo) are, largely, inconclusive. Failed trials represent significant headwinds in treatment development in Psychiatry, because they can erroneously lead to the decision to prematurely end the investigative pursuit of otherwise potentially efficacious therapies.
Therefore, it is imperative that we further increase our understanding of factors which influence signal detection in Psychiatric clinical studies. Several elements have emerged that seem to play a critical role in trial success, gradually reshaping the design of clinical, translational, as well as mechanistic studies in the field. In the present panel, we focus our discussion on four key areas: 1) Subject Selection, 2) Treatment Blinding and Protocol Masking, 3) Subject and Rater Expectations, 4) Site Selection and Geographical Location.

Learning Objectives
1. By the end of this panel, attendees should be able to better understand the relationship between several study design factors and trial outcome in Psychiatric disorders.
2. By the end of this panel, attendees should be able to better understand the relationship between several study execution factors and trial outcome in Psychiatric disorders.

SELECTING PARTICIPANTS FOR CLINICAL TRIALS: HOW TO RECRUIT THE BEST PARTICIPANTS
Madhukar Trivedi, UT Southwestern Medical Center

Individual Abstract: With approximately 50% of randomized clinical trials (RCTs) failing to demonstrate efficacy of a treatment, it is imperative that the research community identify strategies to optimize signal detection. This presentation will focus on research participant

selection as one of the critical steps in optimizing signal detection in antidepressant RCTs. We will specifically focus on four key areas:

1. Refocusing recruitment methods away from simply symptomatic volunteers to treatment-seeking volunteers.

Meeting recruitment goals is often challenging, and requires multiple methods to ensure goals are achieved (Probstfield & Frye, 2011). Often the focal point of a given research study is on finding volunteers who are symptomatic, but the presence of symptoms does not always equate to a willingness to seek treatment. Many investigators now utilize advertisements as a key recruitment source. Published research about optimal recruitment strategies is limited, but a few studies have shown that referrals from other providers lead to higher rates of entering studies than advertisements, although the volume of calls received from advertisements far exceeds direct referrals (Bjornson-Benson, et al., 1993; May et al. 2007). In the STAR*D study, advertising was disallowed to avoid enrollment of "study volunteers (Albert et al., 2006). It is likely that seeking out would-be volunteers who are both symptomatic and who are themselves seeking treatment will result in higher rates of optimal enrollment in research studies.

2. Improving the assessment process (for both diagnostic and outcome assessments) by including independent assessors.

Most assessments in RCTs are conducted either by the investigator or by his or her team of researchers. This is true for the diagnostic assessment for entry into the study, as well as outcomes assessments. Assessments are not 100% accurate by any individual, regardless of experience, and expectation bias may impact participant responses, as well as rater perceptions. Use of independent raters to assess diagnosis, entry eligibility, and outcomes may improve participant selection.

3. Increasing the generalizability of our samples by limiting the exclusion criteria.

Often influenced by sponsors (whether federal or private), inclusion and exclusion criteria are typically quite stringent, and often lead to the exclusion of many participants. While understandable that the investigators and sponsors are attempting to both improve safety and target "clean" participants, generalizability has been compromised. In the STAR*D study, which used much broader entry criteria, almost 80% of enrolled participants would not have met the typical entry criteria for phase III clinical trials (Wisniewski et al., 2009).

4. Expanding our use of biomarkers for research participant selection.

We are entering a new era of personalized medicine, which will require us to examine not only clinical characteristics of patients, but also biological markers (blood-based, neuroimaging, etc.). Prior RCTs have limited inclusion and exclusion to demographic and clinical characteristics, such as symptoms and diseases. New biomarker research results are being reported regularly, yet we have failed to incorporate these findings into our study designs in terms of inclusion. While it is important to increase the generalizability of our samples overall, biomarkers may be a useful method for targeting sub-groups of depressed individuals.

Learning Objectives

1. To review past methods for identifying and recruiting research participants for antidepressant clinical trials.
2. To discuss ways to improve signal detection in antidepressant trials through novel participant selection methods.

Literature References

1. Alpert JE, Biggs MM, Davis L, Shores-Wilson K, Harlan WR, Schneider GW, Ford AL, Farabaugh A, Stegman D, Ritz AL, Husain MM, Macleod L, Wisniewski SR, Rush AJ; STAR*D Investigators. Enrolling research subjects from clinical practice: ethical and procedural issues in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Psychiatry Res 2006;141(2):193-200.
2. Wisniewski SR1, Rush AJ, Nierenberg AA, Gaynes BN, Warden D, Luther JF, McGrath PJ, Lavori PW, Thase ME, Fava M, Trivedi MH. Can phase III trial results of antidepressant medications be generalized to clinical practice? A STAR*D report. Am J Psychiatry 2009; 166(5):599-607.

OPTIMIZING SIGNAL DETECTION IN ANTIDEPRESSANT CLINICAL TRIALS: ROLE OF BLINDING AND MASKING

William Martin, Alkermes, Inc.

Individual Abstract: It is well established that placebo response in antidepressant clinical trials has increased over the last few decades. Over a similar time course, treatment effect sizes have diminished along with the ability of clinical trials to detect drug and placebo differences. To counteract these phenomena, a variety of strategies and design methodologies, such as the double-blind placebo lead-in, have been deployed in attempts to reduce placebo response and/or improve signal detection. More recently, enhanced blinding techniques, also known as masking, have been utilized to enhance signal detection by concealing key study design elements, such as the timing and criteria for randomization, from site staff, subjects and other non-essential trial stakeholders. However, the impact of such design approaches on treatment outcomes and assay sensitivity is unknown. In this session, the enhanced blinding techniques incorporated into recent phase 3 programs for the adjunctive treatment of major depressive disorder will be reviewed and their impact on trial outcomes will be discussed.

Learning Objectives

1. To introduce the audience to the concept of masking key study design elements from clinical trial investigators and staff.
2. Discuss the potential impact of study design masking on clinical trial outcomes in major depressive disorder.

Literature References

1. Bauer M, Pretorius HW, Constant EL, et al: Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. J Clin Psychiatry 2009; 70(4):540-9.
2. Berman RM, Marcus RN, Swanink R, et al: The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007; 68(6):843-53.

HOW SITE SELECTION AND GEOGRAPHIC FACTORS CAN AFFECT SIGNAL DETECTION (AND WHAT MIGHT BE DONE ABOUT IT)

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

Individual Abstract: The progressively greater problems in signal detection in psychopharmacology trials that began in the 1980s and have extended into the 21st century have necessitated serious and sustained efforts to identify critical factors and introduce cost-effective remedies. Among the several critical variables that have been identified, the need to screen individual sites closely and monitor ongoing performance and important regional and

international differences have been recognized. This presentation will highlight key findings from research on novel antidepressants to illustrate the importance of site performance and suggest parameters for good research practices that can reduce or even minimize risks going forward. Improvements in signal detection require ongoing collaboration of investigators and their research staff, sponsors and the clinical research organizations entrusted to implement and oversee the conduct of studies.

Learning Objectives

1. Be familiar with the evidence pertaining to regional and international differences in signal detection.
2. Understand current practices to improve signal detection via site selection and ongoing site monitoring.

Literature References

1. Khin NA, Chen YF, Yang Y, Yang P, Laughren TP. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry. 2011 Apr;72(4):464-72.
2. Undurraga J, Baldessarini RJ. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. Neuropsychopharmacology. 2012 Mar;37(4):851-64.

OPTIMIZING PSYCHIATRIC CLINICAL TRIAL OUTCOMES: THE ROLE OF SUBJECT AND RATER EXPECTATIONS

George Papakostas, Massachusetts General Hospital

Individual Abstract: Psychiatric treatment development has traditionally been hampered by relatively high rates of, so called, "failed" trials. Though "negative" trials (in which it can be concluded with confidence that the experimental treatment is not superior in efficacy to placebo) are informative, failed trials (in which there is a high likelihood that the study, either by design or circumstance, was unable to detect a treatment difference from placebo) are, largely, inconclusive. Failed trials represent significant headwinds in treatment development in Psychiatry, because they can erroneously lead to the decision to prematurely end the investigative pursuit of otherwise potentially efficacious therapies. Therefore, it is imperative that we further increase our understanding of factors which influence signal detection in Psychiatric clinical studies. Several elements have emerged that seem to play a critical role in trial success, gradually reshaping the design of clinical, translational, as well as mechanistic studies in the field. In the present talk, we will focus our discussion on the role of subject and rater expectations.

Learning Objectives

1. By the end of this talk, attendees will better understand the relationship between subject expectations and clinical trial outcome in Psychiatric disorders.
2. By the end of this talk, attendees will better understand the relationship between rater expectations and clinical trial outcome in Psychiatric disorders.

Literature References

1. Papakostas, G.I., Østergaard, S.D., Iovieno, N. (2015). The nature of placebo response in clinical studies of major depressive disorder. Journal of Clinical Psychiatry, 76(4), 456-66.
2. Papakostas, G.I., Fava, M. (2009). Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. European Neuropsychopharmacology, 19(1), 34-40.

CHALLENGES IN TRANSLATING SUICIDALITY CONCEPTS FOR INTERNATIONAL TRIALS ACROSS THE LIFESPAN

Sofija Jovic, MedAvante-ProPhase, Inc.

Overall Abstract: Suicide is a leading cause of premature death among psychiatric patients and a leading source of malpractice suits against psychiatrists and mental health professionals. With the globalization of clinical trials, the need to assess suicidality in a consistent manner across cultures and languages and during the lifespan of the patients has become increasingly important. Thus, how can global trials validly and reliably measure suicidality across ages, countries, and languages? This panel will explore this question by discussing the challenges in measuring suicidality, how measures have to be adapted to children language, and by explaining the process of linguistically validating suicidality scales across languages and cultures. The Sheehan-Suicidality Tracking Scale (S-STS) will be used as an example to discuss these issues. It was developed to provide a brief but efficient assessment instrument for use in assessing change in suicidality (i.e. suicidal ideation, impulses, hallucinations, dreams and behavior) while providing a comprehensive description of suicidality.

The first presentation will discuss the challenges of measuring suicidality. There is a need for a choice of scales to evaluate the full range of suicidality phenomena. Such scales must be capable of use as both safety and efficacy outcome measures in research and in clinical settings. Sensitivity to anti-suicidality effects in modest sample sizes is particularly important in the context of efforts to find and develop anti-suicidality medications. The development of the S-STS will serve as a basis for discussion. The scale has four variants. The standard version of the S-STS is a 16-item scale that assesses the seriousness of suicidality phenomena and the frequency of key phenomena and the overall time spent in suicidality. It is formatted for both clinician- and patient-rating. The Clinically Meaningful Change Measure (CMCM) version of the S-STS is a much more expanded version developed for specific testing of the anti-suicidality effects of medications. With the realization that treatment-emergent suicidality increases with decreasing age under 25 years, in the United States, three pediatric versions of the S-STS were developed (for the 6- to 8-year-olds, the 9- to 12-year-olds, and the13-to 17-year-olds). An adolescent S-STS CMCM version is also available.

The second presentation will show how the S-STS was adapted to the language of pediatric populations. Researchers collaborated with reading specialists who use the sight word lists of Dolch and Fry and the grade level vocabulary lists of Beck, Farr, and Strickland to adapt the adult version to each age group. Examples of how problematic words or phrases were identified and how appropriate words to each age group were substituted to make the questions applicable and relevant to children will be presented. The use of empirically based, age appropriate, linguistic validation of pediatric suicide scales is a necessary step in enhancing their accuracy and comprehension within a single language. The method discussed provides a model for such an approach.

The last presentation will focus on linguistically validating suicidality across languages and countries for clinical trials. Examples taken from the linguistic validation of the S-STS (adult and pediatric versions) in more than 20 languages will be provided. Cultural and semantic challenges as well as involving the author of the scale during the linguistic validation process will also be discussed.

Learning Objectives

1. Attendees will be able to describe the attributes that make valid suicidality scales for use in suicidality trials.
2. Attendees will be able to describe the linguistic validation process of translating suicidality scales for use in clinical trials.

CHALLENGES IN TRANSLATING SUICIDALITY CONCEPTS

David Sheehan, University of South Florida College of Medicine

Individual Abstract: Background: To support pooling of clinical trial data internationally, regulatory agencies, pharmaceutical companies, clinical research organizations, data safety monitoring boards, and medical safety officers are challenged with the difficulty of translating and culturally adapting suicidality assessment outcome measures in a reliable, valid and consistent manner. In psychopharmacology research, serious harm or death by suicide continues to be a leading cause of mortality and morbidity in mental health research and a potential medico-legal liability.

Methods: We explored and reviewed the work of several task forces in providing guidelines, best practices and decision aid tools for the translation and linguistic validation of patient and clinician reported outcomes, to find suitable models to adapt to the needs of translating and linguistically validating suicidality measures. We applied relevant guidelines and best practices in the translation, linguistic validation and both patient and clinician cognitive debriefing of several suicidality measures. The final translations are the result of this iterative process.

Results: Adapting and applying the principles from these guidelines and best practices to suicidality assessment scales is particularly challenging given the sensitivities and stigma (both cultural and religious) around suicide in many cultures. In some languages, the translators and clinician advisors found it challenging to capture the often-subtle nuances of meaning being investigated, since they were unaccustomed to probing these issues in such detail in their clinical assessments. We found that non-suicidal clinicians and translators found the process more challenging to understand than the suicidal patients themselves, who were often more familiar with the raw suicidal experiences. There was more interaction among the translators and consultants on these items than on most symptom items in standard clinical structured diagnostic interviews.

Conclusions: This presentation is designed to assist those in planning multi-national clinical research how to ensure that good research practices are used to properly translate and linguistically validate the full range of core suicidality concepts across languages and cultures. We hope the use of these principles and the lessons learned from this process will lead to greater safety and more sensitive suicidality assessments internationally in clinical trials.

Learning Objectives

1. Be familiar with the challenges in translating suicidality concepts and rating scales into diverse languages and for different cultural and ethnic groups.
2. Be better able to plan for and choose suitable suicidality measures for international clinical trials.

Literature References

1. Sousa, V. D. and Rojjanasrirat, W. (2011), Translation, adaptation and validation of instruments or scales for use in cross-cultural health care research: a clear and user-friendly guideline. Journal of Evaluation in Clinical Practice, 17: 268–274. doi:10.1111/j.1365-2753.2010.01434.x.
2. Wild, D., Eremenco, S., Mear, I., Martin, M., Houchin, C., Gawlicki, M., ... & Cohen, L. (2009). Multinational trials—recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR patient-reported outcomes translation and linguistic validation good research practices task force report. Value in Health, 12(4), 430-440.

LINGUISTIC VALIDATION OF A PEDIATRIC SUICIDALITY SCALE WITHIN A SINGLE LANGUAGE

Darlene Amado, University of South Florida

Individual Abstract: Objective: Findings from the U.S. Food and Drug Administration's meta-analysis of registration trials of antidepressants highlighted that emergent suicidality, under the age of 25 years, increases with decreasing age. With an increased need for meticulous assessment and evaluation of suicidality in children and adolescents, a pediatric suicidality assessment and tracking scale was created utilizing a novel and evidence based approach to its age defined linguistic validation.

Method: Through collaboration with reading specialists, the adult version of the Sheehan-Suicidality Tracking Scale was transformed into pediatric, age group specific, versions by using sight word lists by Dolch and Fry along with grade level vocabulary lists by Farr, Beck and Strickland.

Results: This approach resulted in the creation and documentation of a process for linguistically validating three age-appropriate (6-8yo, 9-12yo and 13-17yo) pediatric versions of the Sheehan-Suicidality Tracking Scale, within a single language, from the adult version of the scale.

Conclusion: To make the pediatric versions of the Sheehan-Suicidality Tracking Scale more reliable, more generalizable, and more useful, further reliability and cognitive debriefing studies are needed in diverse demographic, ethnic, and cultural groups.

Learning Objectives

1. Single Language Linguistic Validation.
2. Linguistic Validation in Children.

Literature References

1. Stone M, Laughren T, Jones ML, et al: Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ; 2009 Aug 11;339:b2880.
2. Hammed T, Laughren T, Racoosin JA: Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry; 2006;63:332–339.

THE PROCESS AND CHALLENGES OF INTERNATIONAL LINGUISTIC VALIDATION OF THE SHEEHAN SUICIDALITY TRACKING SCALE

Caroline Anfray, Mapi Research Trust

Individual Abstract: The Sheehan-Suicidality Tracking Scale (S-STS) was developed to provide a comprehensive description of suicidality (i.e. suicidal ideation, impulses, hallucinations, dreams and behavior) and assess change in suicidality over time. The standard version of the S-STS is a 16-item scale assessing suicidality seriousness on a Likert-type scale (0–4) ranging from "not at all" (0) to "extremely" (4). It is available in adult and pediatric forms (6- to 8-year-olds, 9- to 12-year-olds, and 13-to 17-year-olds). 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 do 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 details in the presentation.

The S-STS was linguistically validated into more than 20 languages, covering America, Europe, South Africa, Asia and Oceania. Examples of challenges encountered during the linguistic validation of the S-STS will be presented. From the "semantic" category of translation issues, several examples will be given. Example 1: How seriously did you think about harming yourself or hurting or injuring yourself …? The major difficulties consisted in finding the right words that would convey all the nuances of the three verbs used in this item, i.e., harming, hurting and injuring. In some languages, only one (e.g., Japanese), or two words (e.g., Cantonese for Hong Kong, French, Malay or Russian) were used. Example 2: How seriously did you think about killing yourself sooner rather than later? Literal translations of "sooner rather than later" often sounded awkward in target languages, and led to the use of paraphrases to convey the concept of urgency or impulsive behavior.

Critical elements in resolving translation difficulties will be discussed, such as the involvement of the author of the scale, i.e., Dr. Sheehan, 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

1. Learn about the linguistic validation process for clinical outcome assessments.
2. Learn about translation challenges with the Sheehan-Suicidality Tracking Scale (S-STS).

Literature References

1. 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.
2. 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.

NEUROPLASTICITY AND KETAMINE RESPONSE IN DEPRESSION

Lawrence Park, NIMH/NIH

Overall Abstract: Neuroplasticity is a natural and continuous process that shapes the structure and function of the brain. As a fundamental mechanism of neuronal adaptation, these processes represent the brain's response to experience, environment and injury. Neuroplasticity may be disrupted in depression, while effective treatment of depression may rely on neuroplasticity mechanisms. For instance, intravenous ketamine has demonstrated rapidly acting and significant improvement in depressive symptoms, and has been associated with various aspects of neuroplasticity.

The term neuroplasticity refers to many distinct but related processes, involving genetic, molecular, cellular and synaptic components. Molecular level brain alterations involve several regulatory mechanisms starting with neurotrophic factors (i.e., brain derived neurotrophic factor [BDNF] a crucial mediator of neuronal plasticity). Intense bidirectional crosstalk occurs between the CNS and immune system (i.e., inflammatory cytokines, nuclear factor – Kappa B). Chemical neurotropic signals lead to structural and functional neuronal changes. Structural alterations are represented by dendritic changes, synaptic remodeling, axonal sprouting, neurite extension, synaptogenesis and neurogenesis. On a functional level, long-term potentiation (LTP) and its converse, long-term depression (LTD), are rapidly evolving, persistent though reversible, activity related mechanisms of synaptic plasticity. This alteration in synaptic strength has been shown to be an important neurophysiological correlate of learning and memory, and is mediated by NMDA dependent phenomena. Technologies have been developed to assess functional alterations in cortical plasticity. These technologies include the application of transcranial magnetic stimulation (TMS) to alter the electrophysiological measures of neuronal functioning, and assessment of MEG gamma power as a correlate of antidepressant response.

Dr. Kadriu will discuss how acute ketamine, a glutamatergic modulator, may interfere in the crosstalk between neuroinflammation and synaptic plasticity, mainly by amelioration of key regulatory elements in the kynurenine pathway, nuclear factor-KappaB, and pro-inflammatory cytokines both in brain and periphery.

Dr. Machado Viera will review the neurotrophic signaling cascade, focusing on BDNF and other neurotropic factors, and their effects on NMDA, AMPA and trkB receptors, and subsequent intracellular effects.

Dr. Daskalakis will introduce the use of transcranial magnetic stimulation (TMS) combined with EMG as a neurophysiological probe to examine plasticity in the motor cortex. In addition he will discuss the use of combined TMS with EEG to evaluate plasticity in the DLPFC and describe how such measures can be used as potential biological markers in the diagnosis and treatment of severe psychiatric disorders.

Dr. Nugent will describe the use of magnetoencephalography (MEG) gamma power as an indicator of neuroplasticity, presenting her findings correlating gamma power with antidepressant response to ketamine administration.

Learning Objectives

1. Understand the different processes involved in neuroplasticity.
2. Understand how ketamine may mediate some neuroplastic processes to achieve antidepressant effect.

NEUROINFLAMMATION AND SYNAPTIC PLASTICITY: DOES KETAMINE TREATMENT MODULATE THE CROSSTALK?

Bashkim Kadriu, National Institute of Mental Health

Individual Abstract: Background: The CNS and immune system are known to engage in an intense bi-directional crosstalk. This highly dynamic model involves glial cells as a crucial element of synapse formation. Specifically, increased activated microglial function as well as impaired astrocytic function likely compromise glutamate reuptake, potentially leading to excitotoxicity in brain. Inflammatory cytokines in brain can influence neurotransmitter release, post-receptor signal transduction mechanisms and, finally, the ability of the synapses to undergo long-term potentiation. Growing evidence suggests that increased psychological stressors and inflammation can interact with a vulnerable genetic background and, by disrupting neurogenesis and neuroplasticity in brain, play a potentially causal role in depression. This symposium will discuss how treatment with the glutamatergic modulator ketamine may better regulate the crosstalk between neuroinflammation and synaptic plasticity, which occurs mainly by ameliorating key regulatory elements in the kynurenine pathway and nuclear factor-Kappa B, as well as altering pro-inflammatory cytokine response both in brain and periphery.

Methods: Pooled data were drawn from previous double-blind, randomized, placebo-controlled, crossover trials designed to test the antidepressant efficacy of ketamine in subjects with major depressive disorder (MDD) and bipolar disorder (BD) as well as healthy controls (HCs). All subjects were medication-free, except for the BD patients who were maintained on therapeutic doses of lithium or valproate. Plasma concentrations of kynurenine pathway analytes (indoleamine 2,3-dioxygenase (IDO), kynurenine (KYN), kynurenic acid (KA), and quinolinic acid (QA)), as well other inflammatory markers (receptor activator for nuclear factor Kappa B ligand (RANKL), TNF-α, IFN-γ, IL-1, etc) were measured at four time points: 60 minutes pre-ketamine infusion (baseline), 230 minutes post-ketamine infusion, on Day 1, and on Day 3 post-ketamine infusion.

Results: Individuals with MDD displayed altered intracellular signaling RANKL, which significantly decreased in response to ketamine (both at 230 minutes and at Day 3 ($p<.001$). In BD subjects, IDO levels were significantly reduced 230 minutes post-ketamine administration ($p=.003$), and remained significantly decreased at Day 1 ($p<.0001$) and Day 3 ($p=.0003$). Inversely, ketamine administration significantly increased both KYN and KA levels at Day 1 and Day 3 (all $p<.01$). No change in QA levels was observed post-ketamine. Interestingly, a post-ketamine reduction in the QA/KYN ratio ($p=.003$) was observed at Day 1 that had a neurotoxic effect on the neuronal cells.

Conclusions: Our findings suggest that, by modulating RANKL, ketamine exerts substantial effects on key regulatory markers that regulate immune response in periphery and the brain. On the other hand, ketamine also downregulated IDO, a marker of microglial activation and a

key rate limiting enzyme of tryptophan catabolism in the kynurenine pathway in the brain. Inversely, it is possible that ketamine may increase hepatic kynurenine production, which would be expected to counter the substantial peripheral proinflammatory state associated with depressive illness. However, increased brain kynurenine production (a marker of astrocyte activation) may also represent a neuroprotective mechanism for restoring astrocytic function that may regulate the clearance of glutamate 'spillover' in the brain.

Learning Objectives

1. The CNS and the immune systems are known to be engaged in an intense bidirectional crosstalk, a highly dynamic model that involves glial cells as a crucial element of the synapse formation.
2. Treatment with ketamine, a glutamatergic modulator, may interfere in the crosstalk between neuroinflammation and synaptic plasticity, mainly by amelioration of key regulatory elements in the kynurenine pathway, nuclear factor-KappaB, and pro-inflammatory cytokines both in brain and periphery.

Literature References

1. Di Filippo M, Sarchielli P, Picconi B, Calabresi P. Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centred, therapeutic approach to neurological disorders. Trends Pharmacol Sci. 2008;29(8):402-412.
2. Miller AH. Conceptual confluence: the kynurenine pathway as a common target for ketamine and the convergence of the inflammation and glutamate hypotheses of depression. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2013;38(9):1607-1608.

BIOMARKERS OF KETAMINE'S RAPID ANTIDEPRESSANT EFFECTS: FOCUS ON NEUROPLASTICITY

Rodrigo Machado-Vieira, McGovern Medical School, University of Texas Science Center in Houston

Individual Abstract: The current presentation aims to provide an overview of the main findings related to activation of intracellular signaling and increased neurotrophic factors levels associated with the rapid antidepressant effects of ketamine. Increased plasma BDNF levels and other proteins related to activation of cellular plasticity within the intracellular signaling cascade will be presented. Also, these plasticity-related proteins seem to also predict the rapid efficacy of ketamine. The present results highlight the role of blood plasticity makers in the rapid antidepressant efficacy of ketamine and the need for valuable predictors of ketamine response in the context of personalized medicine.

Learning Objectives

1. Provide an overview of the role of plasticity in the rapid antidepressant effects of ketamine.
2. Provide insights into the role of glutamate metabolism in the regulation of intracellular signaling and activation of plasticity pathways.

Literature References

1. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist.Machado-Vieira R, Yuan P, Brutsche N, DiazGranados N, Luckenbaugh D, Manji HK, Zarate CA Jr.J Clin Psychiatry. 2009 Dec;70(12):1662-6.

2. Ketamine: translating mechanistic discoveries into the next generation of glutamate modulators for mood disorders.Zarate CA Jr, Machado-Vieira R. Mol Psychiatry. 2017 Mar;22(3):324-327. doi: 10.1038/mp.2016.249.

MEASURING NEUROPLASTICITY IN THE DLPFC USING TMS COMBINED WITH EEG

Zafiris Daskalakis, CAMH

Individual Abstract: by altering its physiological, molecular and structural features. The pathophysiology of schizophrenia and depression is closely associated with deficits in the molecular mechanisms that mediate plasticity (i.e., NMDA, GABA, serotonin and dopamine). In the human motor cortex, plasticity can be produced through repetitive TMS (rTMS) and through paired associative stimulation (PAS). We have previously demonstrated that plasticity in the motor cortex is disrupted in schizophrenia relative to healthy subjects and is also disrupted by excess alcohol intake. We have also recently demonstrated that plasticity can be produced in the DLPFC through PAS and through rTMS and measured using combined TMS with EEG. For this symposium, I will present data demonstrating the induction of plasticity in the DLPFC and how such plasticity can be disrupted by various pharmacological strategies. I will also demonstrate data linking the induction of neuroplasticity in the DLPFC through magnetic seizure therapy. I will also discuss how these plasticity measures can be used as a biomarker for novel treatments (i.e., rTMS and MST). In summary, this presentation will provide important insights linking plasticity to the pathophysiology of severe psychiatric disorders and how measuring plasticity can serve as a potential biomarker of therapeutic change.

Learning Objectives

1. Understand how to measure neuroplasticity in the human prefrontal cortex.
2. Understand how neuroplasticity is disrupted in the human prefrontal cortex.

Literature References

1. Rajji TK, Sun Y, Zomorrodi-Moghaddam R, Farzan F, Blumberger DM, Mulsant BH, Fitzgerald PB, Daskalakis ZJ. PAS-induced potentiation of cortical-evoked activity in the dorsolateral prefrontal cortex. Neuropsychopharmacology. 2013;38:2545-2552.
2. Sun Y, Farzan F, Mulsant BH, Rajji T, Fitzgerald PB, Barr MS, Downar J, Wong W, Blumberger DM, Daskalakis ZJ. Predicting Remission of Suicidal Ideation Following Magnetic Seizure Therapy in Patients with Treatment-Resistant Depression. JAMA psychiatry. 2016;in press.

DISTINCT BEHAVIORAL AND ELECTROPHYSIOLOGICAL EFFECTS OF KETAMINE IN DEPRESSED PATIENTS AND HEALTHY VOLUNTEERS

Allison Nugent, Experimental Therapeutics and Pathophysiology Branch, NIMH, NIH, DHHS

Individual Abstract: Purpose: The purpose of this study was to replicate the finding of a rapid antidepressant effect of ketamine in patients with treatment resistant major depressive disorder (TRD), as well as to observe the effects of ketamine in a healthy population. We also sought to examine the relationship between the antidepressant response and gamma power. Multiple synaptic mechanisms contribute to the generation of gamma oscillations, including AMPA receptor related depolarization and GABAA receptor mediated inhibition. Ketamine may act on both of these, by reducing inhibition from GABAergic interneurons, increasing glutamate release and enhancing AMPA throughput. Because gamma oscillations are intimately related

to inhibition/excitation balance, they can potentially be used as a proxy for homeostatic balance.

Methods: Thirty-five unmedicated patients with TRD and 25 healthy controls enrolled in a double-blind placebo-controlled randomized cross-over trial of 0.5 mg/kg IV ketamine. At baseline, and between six and nine hours following both infusions, subjects underwent magnetoencephalography (MEG) recording during rest. Artifact free epochs from each recording were projected into anatomical space using synthetic aperture magnetometry (SAM). Normalized gamma power images were analyzed using linear mixed models; the change in gamma power between ketamine and placebo sessions is reported. The relationship between gamma power and antidepressant response was also assessed.

Results: MDD subjects showed significant improvements in depressive symptoms. Healthy control subjects exhibited modest but significant increases in depressive symptoms for up to one day after ketamine administration, primarily in the domains of anhedonia and anxiety. Both groups showed increased resting gamma power following ketamine. In MDD subjects, gamma power was not associated with the magnitude of the antidepressant effect. However, additional exploratory tests found that baseline gamma power moderated the relationship between post-ketamine gamma power and antidepressant response. Specifically, higher post-ketamine gamma power was associated with better response in MDD subjects with lower baseline gamma, with an inverted relationship in MDD subjects with higher baseline gamma. This relationship was observed in multiple regions involved in networks hypothesized to be involved in the pathophysiology of MDD.

Discussion: Our findings replicated past findings of ketamine's rapid antidepressant effect in TRD. We extended these findings by demonstrating a significant increase in depressive symptoms in healthy subjects. Although ketamine infusion has been used extensively in healthy subjects as a model for schizophrenia, our results suggest that this may be less than ideal. This study is also the first to demonstrate that gamma power remains increased in subjects six to nine hours after ketamine infusion. Our finding that baseline gamma moderates the relationship between the increase in gamma power post-ketamine and the antidepressant response suggests that resting gamma oscillations may be a proxy measure of inhibition/excitation balance and homeostasis. This adds to the literature characterizing depression as a disorder of homeostatic regulation.

Learning Objectives

1. Understand the behavioral and electrophysiological effects of ketamine infusion as compared to placebo infusion in patients with treatment resistant depression, and healthy volunteers.
2. Understand the homeostatic regulatory hypothesis of major depression, and how this study relates to that theory.

Literature References

1. Shaw AD, Saxena N, E Jackson L, et al: Ketamine amplifies induced gamma frequency oscillations in the human cerebral cortex. Eur Neuropsychopharmacol 2015; 25(8):1136-46.
2. Zarate CA Jr., Singh JB, Carlson PJ, et al: A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63:856-864.

CONTROVERSIES IN BIPOLAR DEPRESSION ACROSS THE LIFESPAN*

Scott Aaronson, Sheppard Pratt Health System

Overall Abstract: Bipolar depression presents unique challenges for both researchers and clinicians. Despite it being the most common presentation for bipolar disorder, there is only a small and often conflicting database for what best practices should be. There is a growing population of pediatric and geriatric patients presenting with bipolar depression. Each of these groups present their own challenges and represent the theme of this year's meeting. Several recognized experts in bipolar depression will be outlining the key challenges in the field and will provide insight from both a clinical and scientific perspective. Starting the panel will be Dr. Robert Post who will offer his perspective on why there is an increase in the presentation of pediatric bipolar disorder in the US but not in some other developed countries and why this seems to lead more to delayed treatment and the risk of poorer outcomes. He will be followed by Dr. Trisha Suppes who has published extensively on the most confusing question of all in bipolar depression--should we be using antidepressants? She will offer her vision of what the answer may be to this critical question. Next, Dr. Aaronson will discuss recent findings in the use of neurostimulation (Transcranial Magnetic Stimulation and Vagus Nerve Stimulation) in both the long and short term management of bipolar depression. Neurostimulation may enhance outcomes in a way pharmacologic interventions are unable to. Finally, Dr. Martha Sajatovic will discuss the growing population of seniors with bipolar disorder. Geriatric bipolar disorder also comes with the complications of medical comorbidities and greater likelihood of drug interactions. Dr. Sajatovic will review the current treatment recommendations applicable to this especially vulnerable population.

Learning Objectives

1. Recognize the challenges and treatment needs presented by growing populations of pediatric and geriatric bipolar patients.
2. Describe the current perspectives on the use of antidepressants and neurostimulation treatments in the management of bipolar depression.

MORE CHILDHOOD ONSET BIPOLAR DISORDERS IN THE U.S.: WHAT YOU NEED TO KNOW AND DO

Robert Post, Bipolar Collaborative Network

Individual Abstract 968 outpatients with bipolar disorder participated in our Bipolar Collaborative Network with 4 sites in the US (L. Altshuler, M. Frye, T. Suppes, S. McElroy, P Keck, R. Post, & G Leverich) and 3 in the Netherlands (W. Nolen and R. Kupka) and Germany (H. Grunze). US patients had more early onsets (2/3 before age 19), more childhood adversities, more alcohol and substance abuse, more episodes and rapid cycling, and more treatment refractoriness in naturalistic follow up. 4 generations of their relatives had a higher incidence of family history positive for depression, bipolar, alcohol and substance abuse, suicide attempts, and "other" illness. These included: 4) grandparents, 3) parents, 2) selves, siblings, and spouses, and 1) offspring. Thus, US compared to the European patients had both greater genetic and environmental vulnerability factors. There were longer delays to first treatment, and this and early onset are both risk factors for a poor outcome in adulthood.

Given this perspective, earlier recognition and treatment is critical to beginning to address this life altering situation. Parental bipolar disorder is a risk factor for childhood onset bipolar disorder, but even more so is a history of 3 or more relatives with a mood disorder or 3 or more generations positive for a mood disorder. For those at high risk, good diet, exercise,

mindful/meditation, and music training should be started; for those with prodromal symptoms, psycho-education and family focused therapy (FFT) should be added. Those with BP-NOS should be treated as vigorously with pharmacotherapy as those with BP I or BP II, and often complex combination therapy will be required. The illness has been grotesquely under studied, such that guidelines are inadequately informative, and a child's response to medications should be carefully monitored and used as the basis for further therapeutic efforts. Parents of children (2-12) can join a Child Network so that they can rate on a secure website their child's severity of anxiety, depression, ADHD, oppositional behavior, and mania on a weekly basis. The ratings can then be printed out to take to clinicians for ease of evaluation of symptom course, need for treatment, and effectiveness of any treatment given. Consent and joining the Network is available at www.bipolarnews.org (click on Child Network).

Learning Objectives

1. Review the evidence for the large burden of childhood onset bipolar disorder and its many comorbidities in the US.
2. Discuss ways of ameliorating this illness burden by generating more clinical research and initiating earlier and more effective treatment.

Literature References

1. Post RM, Altshuler LL, Kupka R, McElroy SL, Frye MA, Rowe M, Grunze H, Suppes T, Keck PE, Jr., Leverich GS, Nolen WA. More childhood onset bipolar disorder in the United States than Canada or Europe: Implications for treatment and prevention. Neuroscience and biobehavioral reviews. 2017;74:204-213.
2. Post RM. Epigenetic basis of sensitization to stress, affective episodes, and stimulants: implications for illness progression and prevention. Bipolar disorders. 2016;18:315-324.

ANTIDEPRESSANTS TO BE OR NOT TO BE: WHEN IN BIPOLAR DEPRESSION SHOULD WE USE THEM?

Terence Ketter, Stanford University School of Medicine

Individual Abstract: Antidepressants are an important advance in our armamentarium of options for managing a myriad of psychiatric symptoms including depression, anxiety, and other anxiety disorders. There use in patients with bipolar disorder continues to be controversial and often debated.

The earliest use of antidepressants in bipolar depression by Himmelhoch and others demonstrated efficacy and high switch rates in bipolar I populations when antidepressants were given without mood stabilizers. It should perhaps be noted that the patients of the 1970's and 1980's were more often the most classic presentations of bipolar I and not the more complex and co-morbid population we currently diagnose under bipolar I disorder. Since these early days showing high switch rates, up to 30% and more, a concern has been enduring about the potential deleterious impact of antidepressants in the short and long term, as well as debate as to their utility. Despite ongoing active debate and articles showing both positive and negative data the use of antidepressants continues to be very high in treatment of mood disorders. In particular, the question if patients with bipolar I versus bipolar II may in fact have different responses and liability warrants further exploration.

In this symposium, I will focus on recent studies that provide a control group for comparison reviewing data on treatment with antidepressants in bipolar I and II disorders. The recently

published Altshuler trial in the acute treatment of bipolar II depression (2017) suggest that unopposed antidepressants may have a very different result from the earlier work done in patients with bipolar I disorder with no mood stabilizers on board. This recent trial and ongoing work by Amsterdam and others in assessing best treatments for bipolar II will be reviewed. These studies will be contrasted to the studies in patients with bipolar I disorder where controlled studies have shown little to no impact of antidepressants in clinical trials.
Consideration of where studies are most needed in assessing the utility of antidepressants will be discussed. In this consideration will be if follow-up studies are warranted on several case series that suggest discontinuation of antidepressants following apparent response may lead to higher episode recurrence. Finally, an overview of guidelines recommendations on the use of antidepressants for bipolar disorder will be provided, including the comprehensive International Society of Bipolar Disorders Task Force publication on this issue (2013) and the recently completed updated CANMAT Guidelines (2018).

Learning Objectives

1. Understand the response to antidepressants may be different in patients with bipolar I versus bipolar II disorders.
2. Consider in light of clinical trials and guideline recommendations when it is most appropriate to use antidepressants for bipolar depression.

Literature References

1. Altshuler L, Sugar C, McElroy S, Calimlim B, Gitlin M, Keck P, Aquino-Elias A, Martens B, Fischer E, English T, Roach J, Suppes T. Switch rates during acute treatment for bipolar II depression with lithium, sertraline or the combination for bipolar II depression: a randomized, double-blind comparison. Am J Psychiatry. October 2016.
2. Pacchiarotti, I. et al. The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders. Am J Psychiatry 170, 1249–62 (2013).

TRANSCRANIAL MAGNETIC STIMULATION AND VAGUS NERVE STIMULATION IN THE ACUTE AND CHRONIC MANAGEMENT OF BIPOLAR DEPRESSION

Scott Aaronson, Sheppard Pratt Health System

Individual Abstract: Neurostimulation techniques may provide a unique option for the management of bipolar depression. The brain is as much electrical as it is chemical, yet the majority of somatic interventions for bipolar disorder are chemically based. Medications have proven more effective for the management of manic and not depressive symptoms. FDA approved medications for bipolar depression include three atypical antipsychotics, one in combination with an antidepressant. Controversy abounds with regard to the use of antidepressants in bipolar disorder. There is emerging evidence that Transcranial Magnetic Stimulation (TMS) may provide relief in acute bipolar depression and Vagus Nerve Stimulation (VNS) may be useful in long term management.
A retrospective analysis of 39 bipolar depressed patients receiving left dorsolateral prefrontal cortex stimulation at 10HZ for 4 seconds, every 30 seconds for 37.5 minutes demonstrated a 69% response rate by MADRS criteria and a 35% remission rate with better results in the bipolar I than the bipolar II population (72% vs. 67% response rate) but a higher

discontinuation rate (17% vs. 5%). While these are preliminary, open label results, they are consistent with other studies in the field and may represent an opportunity to provide targeted, episode driven, non-systemic support for acute bipolar depressive episodes.
A large naturalistic study of patients with severe treatment resistant depression compared the use of VNS vs. treatment as usual (TAU). This 800 patient study included 117 patients with bipolar depression, 94 of them received VNS and 23 received treatment as usual. These patients failed at least 4 antidepressants and an average of 8. The cumulative response rate over a five year period was 70.5% for the VNS group and 37.6% for the TAU group with a calculated NNT=3.
There is preliminary evidence that TMS may provide important support for bipolar depressive episodes though this needs to be proven with randomized sham controlled trials. Evidence for the utility of VNS for the chronic management of bipolar depression in a large population suggests it should be more available for use given that it is an FDA approved indication.

Learning Objectives

1. Describe potential benefits of the use of TMS in the acute management of bipolar depression.
2. Identify patients for whom the use of VNS in bipolar disorder may be helpful.

Literature References

1. Aaronson ST, Sears P, Ruvuna et. al., A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. Am J Psychiatry. Jul 1;174(7):640-648 2017.
2. McGirr A, Karmani S, Arsappa R, et al: Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. World Psychiatry 15(1):85–86, 2016.

BIPOLAR DEPRESSION IN OLDER ADULTS

Martha Sajatovic, University Hospitals Case Medical Center

Individual Abstract: Lithium and select anticonvulsants and antipsychotic medications are all gold-standard and first-line treatment for bipolar disorder (BD) in the general population. However, in older-age bipolar disorder (OABD), the role of specific compounds is less clear. There is only one prospective randomized, controlled trial specific to OABD that can inform a relative assessment of benefits vs. burden of lithium vs. divalproex, and this was conducted in patients with Type 1 Bipolar mania. That said, an emerging body of literature suggests interventions and management approaches that may benefit older individuals with bipolar depression. A recent review of 34 treatment guidelines from 19 countries found that recommendations for choosing medications for geriatric bipolar disorder are generally similar to recommendations for younger adults, with the caveat that general medical comorbidity and concomitant medications can render older adults more vulnerable to adverse effects. For BD depression there is positive efficacy data supporting the use of lamotrigine, lurasidone quetiapine, and asenapine. Effective dosing in older adults samples is almost uniformly lower than with younger BD patients. As with younger patients, poor adherence to prescribed maintenance antipsychotic is pervasive in late-life BD, with nearly 1 in 2 individuals meeting thresholds for sub-optimal adherence. Some psychosocial approaches can improve depression symptoms and promote medication adherence. ECT is an additional consideration for geriatric patients with refractory BD depression.

Adverse drug reactions are a general concern with advancing age and side effects of particular relevance to BD elders with depression include; 1.) Increased risk of sedation, cognitive effects and falls with nearly all BD drugs, 2.) Elevated risk for metabolic abnormalities, extrapyramidal symptoms and tardive dyskinesia with antipsychotic drugs; and 3.)Renal deterioration with lithium. It is not clear how the general risk of premature mortality for older individuals with dementia treated with antipsychotics may apply to OABD. An additional debate is whether sustained lithium therapy may provide neuroprotective effects and potentially prevent dementia occurrence or progression, a drug-related "side effect" that may be particularly relevant in OABD. In conclusion, while data from uncontrolled trials and secondary data analyses suggest standard pharmacotherapies can reduce symptoms of depression in OABD, more data is needed specific to this vulnerable population.

Learning Objectives

1. Participants will gain familiarity with treatment data specific to older-age bipolar disorder.
2. Participants will better understand the risk vs. benefit burden for pharmacotherapies in older bipolar depressed patients, particularly as relates to drug side effects and the extensive medical comorbidity typically seen in this population.

Literature References

1. Dols A, Kessing L, Strejilevich S, Rej S, Tsai SY, Gildengers A, Ameida OP, Shulman K, Sajatovic M. Do Current National and International Guidelines Have Specific Recommendations for Older Adults with Bipolar Disorder? A Brief Report. International Journal of Geriatric Psychiatry, 31(12):1295-1300, 2016. doi: 10.1002/gps.4534.
2. Sajatovic M, Forester B, Tsai J, Kroger H, Pikalov A, Cucchiaro J, Loebel A. Efficacy of Lurasidone in Adults Aged 55 Years and Older With Bipolar Depression: Post Hoc Analysis of 2 Double-Blind, Placebo-Controlled Studies. J Clin Psychiatry, 77(10):e1324-e1331, 2016.

Regulatory Wrap-Up Plenary
10:15 a.m. - 11:45 a.m.

REGULATORY WRAP-UP SESSION

John Newcomer, Charles E. Schmidt College of Medicine, Florida Atlantic University

Overall Abstract: Participants will be able to ask questions to a panel of EMA and FDA representatives.

Tiffany Farchione, US Food and Drug Administration
Mitchell Mathis, FDA
Valentina Mantua, AIFA